# Chemoenzymatic Synthesis of $C_2$ Symmetric Chiral Dienes for Asymmetric Catalysis

UNIVERSITY OF
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Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

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**Abstract**

Chiral bicyclic dienes have shown novel enantioselectivity and activity in asymmetric catalytic reactions. However, access to the most useful $C_2$-symmetric dienes, such as 2,5-diaryl[2.2.2]bicyclo-2,5-dienes developed by Hayashi *et al.*, is limited. The chiral 2,5-diketone synthetic precursors to the dienes are difficult to access both in terms of synthesis and resolution. This has limited the application of the diene ligands in asymmetric catalysis.

A practical synthetic route for the preparation of chiral bicyclo[2.2.2]octane-2,5-dione, the precursor for Hayashi's ligand, was realized *via* Diels-Alder reaction and kinetic resolution of an enol acetate derivative by immobilized lipases.

A chemoenzymatic approach giving access to a new series of chiral 1,4-disubstituted $C_2$-symmetric [2.2.2] diene ligands was developed. The scalability and ease of operation of the key enzymatic resolution step, in addition to high yielding chemical transformations, provides a highly practical route that could quickly satisfy demands for greater quantities. Moreover, a significant electronic effect was observed in the diene ligands for rhodium-catalyzed arylation reactions. Both catalytic activity and, more interestingly from a mechanistic perspective, enantioselectivity depends on the electronic properties of the ligands.

## Abbreviations

| | |
|---|---|
| ACA | Asymmetric conjugate addition |
| acac | Acetylacetonate |
| AIBN | Azo-bis-isobutryonitrile |
| BINAM | 2,2'-bis (amino)-1,1'-binaphthyl |
| BINAP | 2,2'-bis (diphenylphosphino)-1,1'-binaphthyl |
| CAN | Ceric ammonium nitrate |
| Cat. | Catalytst |
| CSA | 10-camphorsulfonic acid |
| COT | 1,3,5-cyclooctatrienyl |
| COD | 1,5-Cylcooctadiene |
| Cp | Cyclopentadienyl |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| dba | Dibenzylidene acetone |
| DBN | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DBU | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DMF | *N,N*'-dimethylformamide |
| DMAP | 4-dimethylaminopyridine |
| DME | 1,4-dimethoxyethane |
| DPEN | (*R,R*) or (*S,S*)-1,2-Diphenyl-1,2-ethanediamine |
| dppb | 1,4-bis (diphenylphosphino)butane |
| dppe | 1,2-bis (diphenylphosphino)ethane |
| dppf | bis (diphenylphosphino)ferrocene |
| e.e. | enantiomeric excess |
| EDA (en) | ethylenediamine |
| Fc | ferrocenyl |
| GC | Gas chromatography |
| h | hours |
| *hv* | Irradiation with light |

| | |
|---|---|
| HPLC | High performance liquid chromatography |
| *i*-Pr | isopropyl |
| LAH | Lithium aluminum hydride |
| LDA | Lithium diisopropylamide |
| LHMDS | Lithium hexamethyldisilazide |
| *m*-CPBA | *meta*-cholorperoxybenzoic acid |
| MOM | methoxymethyl |
| M.S. | Molecular sieves |
| NBD | Norbornadiene |
| NBS | N-Bromosuccinimide |
| NaPi | Sodium phosphates buffer system |
| *n*-BuLi | *n*-butyllithium |
| PCC | Pyridinium chlorochromate |
| PDC | Pyridinium dichromate |
| PEG | Polyethylene glycol |
| PPL | Porcine pancreatic lipase |
| PFL | *Pseudomonas fluorescens* lipase |
| Py | Pyridine |
| quant. | quantitative yield |
| TBAF | Tetrabutylammonium fluoride |
| TEMPO | Tetramethylpiperdinyloxy free radical |
| TLC | Thin layer chromatography |
| Tf | Triflate |
| TMEDA | Tetramethylethylenediamine |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TMS | Trimethylsilyl |
| Ts (Tos) | Tosyl (p-toluenesulfonyl) |
| w.r.t. | with regard to |

## Content

# Chapter 1 Introduction

## 1.1 Brief introduction to the history of olefin-metal complexes

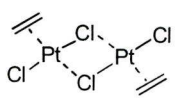
The first example of metal-olefin complexes that can be recognized in literature is Zeise's salt which was disclosed by Danish pharmacist Zeise in 1827[1]. The stoichiometry of this compound was characterized as $K[PtCl_3 \cdot C_2H_2] \cdot H_2O$. Although compounds with transition metal bonds had been known for many years, the real structures of these complexes including the Zeise's salts were not settled until 1950s [2]. In 1975, the 3-dimension structure of the Zeise's salt was elucidated by X-ray diffraction [3].

A landmark compound, which inflated the study of *d*-block metals-hydrocarbon complexes, was the ferrocene, first disclosed in 1951 by Pauson and Kealy [4]. Although the structure of ferrocene was correctly deduced by Wilkinson and Woodward soon after its disclosure[5], direct elucidation of the structure of ferrocene was confirmed by NMR spectroscopy and X-ray crystallography in 1956[6], five years after ferrocene was discovered. With the help of modern technology, NMR and X-ray diffraction, a large number of olefin-metal complexes have been synthesized and characterized. These complexes are of great importance in homogeneous chiral or achiral catalysis because they are convenient catalyst precursors that are easily exchanged with stronger coordinating ligands or cleaved by reactants.

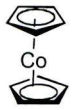
The olefin-metal complexes shown in ***Table1.1.1*** [7-16] are representative of transition metals, some of which are commercially available and widely used in varies reactions from laboratory to industrial scale. For examples, after the COD moiety is replaced by BINAP and chloride is removed by an non-coordinating conterion in compound **4**, it serves as the catalyst for producing the key intermediate of L-menthol in thousands of tons a year at Takasago[17]. Complex **5** is currently widely used in a broad range of rhodium-catalyzed asymmetric catalysis after the ethylene moieties are exchanged by chiral ligands [18]. Complex **6** has been successfully used for asymmetric transfer hydrogenation which when combined with chiral ligands [19, 20]. The palladium species **7** is a convenient phosphine free Pd(0) source, often used as a

precursor for cross-coupling reactions[21], [22], and the Pt compound **8** is also known as Karstedt's catalyst which is used to produce vinylsilanes on an industrial scale[23].

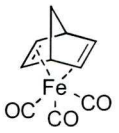
***Table 1.1.1*** Representative Olefin Complexes of Transitation Metals



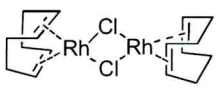
$[PtCl_2(C_2H_4)]_2$
**1** (ref. 7)
Zeise's dimer



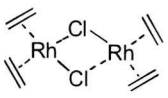
$[Co(\eta5\text{-}C_5H_5)_2]$
**2** (ref. 8, 9)
Bis(cylcopentadienyl)colbalt(II)



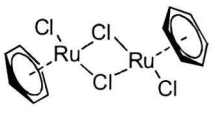
$[Fe(nbd)_2(CO)_3]$
**3** (ref. 10)
Tricarbonyl(norbornadiene)iron(0)



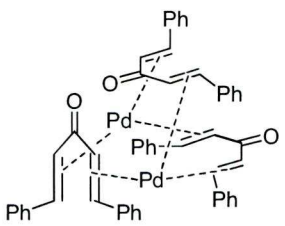
$[RhCl(COD)]_2$
**4** (ref. 11)
Chloro(cyclooctadiene)
Rhodium(I) dimer



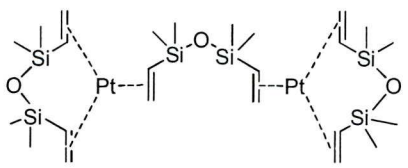
$[RhCl(C_2H_4)_2]_2$
**5** (ref. 12)
Chloro(bisethylene)
Rhodium(I) dimer



$[RuCl_2(\eta6\text{-}C_6H_6)]_2$
**6** (ref. 13)
Dichloro(benzene)Ruthenium(II) dimer



$Pd_2dba_3$
**7** (ref. 14, 15)
Tris(dibenzylideneacetone)dipalladium(0)



$Pt_2(dvds)_3$
**8** (ref. 16)
Karstedt's catalyst

Although a few olefin complexes of transition metals had been known for many years since the discovery of Zeise's salts, it was only in 1950s, after the intense research following the discovery of ferrocene, that it became recognized that the formation of bonds to olefins is an general and characteristic property of all *d*-group transition metals. Walsh introduced the concept of Lewis acid / Lewis base to the olefin / metal bond [24] and this view was refined by Dewar by using Molecular Orbital Theory [25]. In this view (illustrated in ***Fig. 1.1.1***), the metal to olefin bond consists of two parts: (a) overlap of the π-electron density of the olefin with a σ-type acceptor orbital

on the metal atom; (b) a "back-bond" resulting from flow of the electron density from filled metal $d_{xy}$ or other $d\pi$-$p\pi$ hybrid orbitals into anti-bonding orbitals on the carbon atoms.

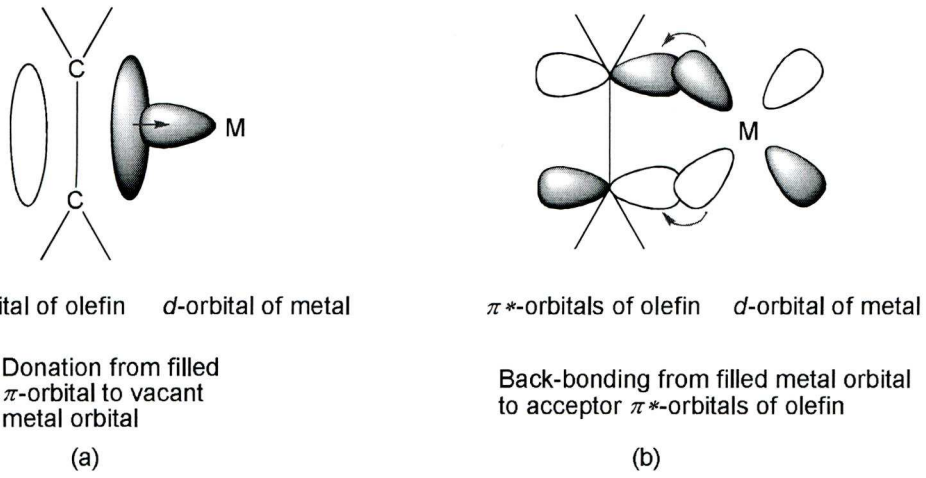



***Fig. 1.1-1*** Models showing the molecular orbital view of olefin-metal bonding according to Dewar. The donor part of the bond is shown in (a), and the back-bonding part in (b).

It is generally accepted that an increase in the back donation would increase the stability of an olefin-metal complex, because increasing back-donation will strengthen the σ-type back-bonding. As a result that will cause the hybridization of the coordinated olefin carbon center to become more like $sp^3$ [18]. An estimate for the degree of back-donation can be related to the coordination shift $\Delta\delta$ ( $\Delta\delta = \delta_{complex} - \delta_{freeligand}$) observed by $^{13}C$ NMR [26].

Pioneering work on the investigation into the stabilities of olefin complexes of transition metals has been done by Cramer [27] and Volger [28]. By comparing a series of mono enes in an exchange reaction with $[Rh(C_2H_4)_2acac]$, it was found that the relative stabilities of olefin-metal complexes were both sterically and electronically sensitive, particularly the latter. Generally, the stabilities were enhanced by electron-withdrawing substituent groups on the olefin, which was reflected by the large equilibrium constant for 1,2-difluoroethlyene (see ***Table 1.1.2*** entries 8 and 9) [27].

***Table 1.1.2*** Equilibrium constants of olefin exchange with [acacRh($C_2H_4$)$_2$]

$$\text{Olefin} + [\text{acacRh}(C_2H_4)_2] \overset{K_{eq.}}{\rightleftharpoons} [\text{acacRh}(C_2H_4)(\text{Olefin})] + C_2H_4$$

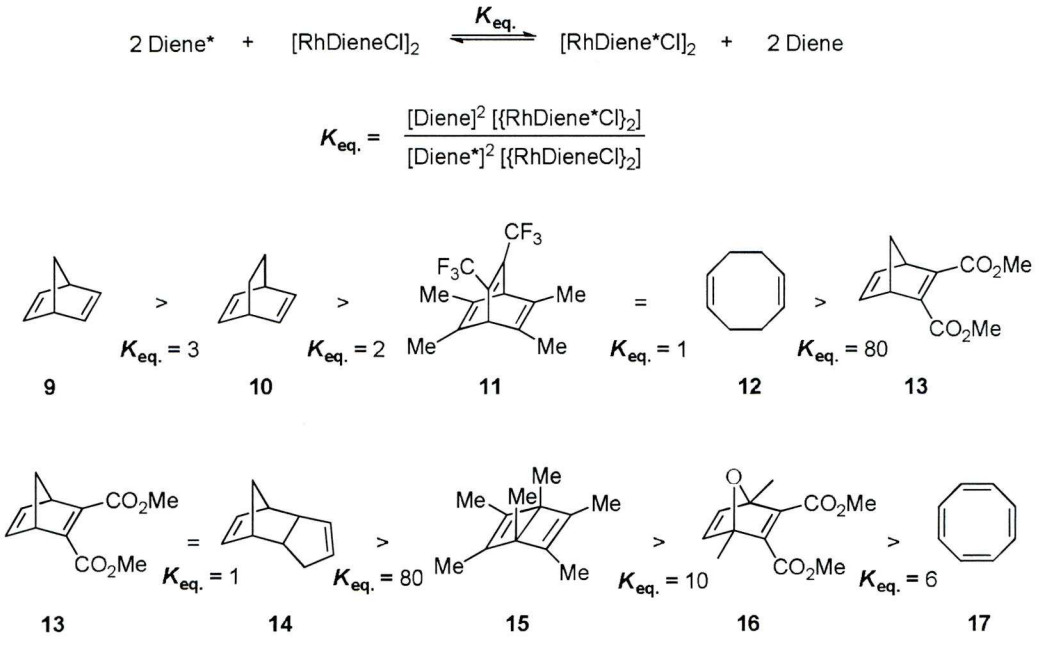
$$K_{eq.} = \frac{[\text{acacRh}(C_2H_4)(\text{Olefin})]\,[C_2H_4]\,f_{C_2H_4}}{[\text{acacRh}(C_2H_4)_2]\,[\,\text{Olefin}]\,f_{\text{Olefin}}}$$

| Entry | Olefin | $K_{eq.}$ |
|---|---|---|
| 1 | $H_2C{=}CHCH_3$ | 78 ± 7 |
| 2 | $H_2C{=}CHC_2H_5$ | 92 ± 18 |
| 3 | *trans*-$H_3CHC{=}CHCH_3$ | 4.1 ± 0.3 |
| 4 | *cis*-$H_3CHC{=}CHCH_3$ | 2.0 ± 0.3 |
| 5 | $H_2C{=}CCH_3CH_3$ | 0.35 ± 0.02 |
| 6 | $H_2C{=}CHCl$ | 170 ± 19 |
| 7 | $H_2C{=}CHF$ | 320 ± 22 |
| 8 | *trans*-$FHC{=}CHF$ | 1240 ± 360 |
| 9 | *cis*-$FHC{=}CHF$ | 1590 ± 330 |
| 10 | $H_2C{=}CF_2$ | 100 ± 10 |
| 11 | $H_2C{=}CHOCH_3$ | 18 ± 2 |

On the other hand, the fluoronated olefins show much lower rate in the displacement reactions in ***Table 1.1.2*** than propene or butane, which coordinate weakly. From this it was inferred that formation of a π back-bond plays a minor role in the development of the transition state for nucleophilic olefin exchange. All these results implied that (1) the π back-bonding governs the stabilities of olefin-rhodium complex, (2) although electro-poor olefin- rhodium complexes were thermodynamically favored due to the higher stabilities (attributed to the stronger back-bonding), they were kinetically disfavored due to the weaker nucleophilicity.

Volger's work shows that for the rigid olefins, the unique geometry of bicyclic dienes can give a great increase in stability even there are no electron-withdrawing substitutuents on the alkene. Of the nine olefins shown in ***Scheme 1.1.1***,

bicyclo[2.2.1]hepta-2,5-diene (**9**) and bicyclo[2.2.2]octa-2,5-diene (**10**) form the most stable complexes with rhodium. According to the author, it was concluded that the geometry of the chelating diene and the electronic and steric effects of its substituents primarily determine the coordination ability towards rhodium(I). The unique stability of the rhodium complex with **9** or **10** is attributed to the release of the ring tension of these rigid dienes. It is suggested again that the strength of the rhodium olefin coordinating bond is also mainly governed by the π back-bonding character of the diene [28].



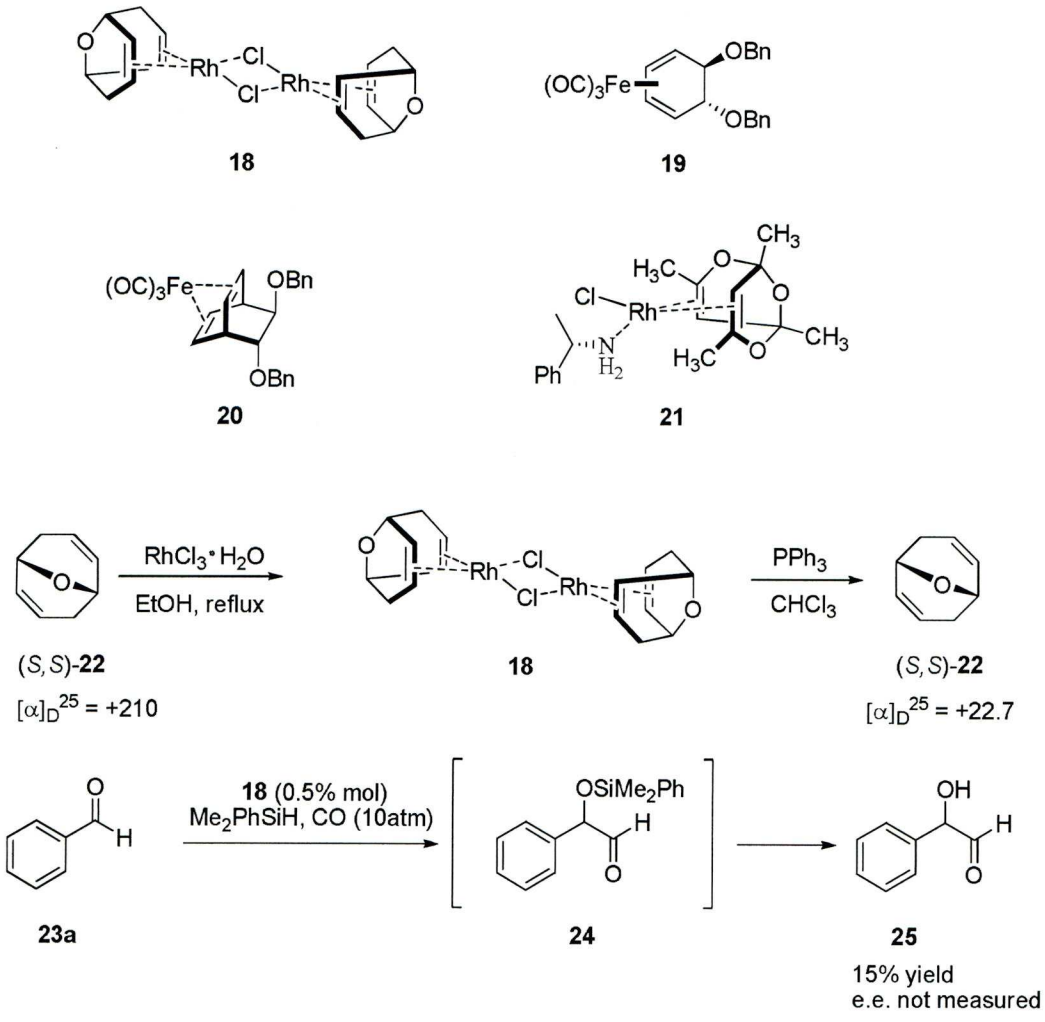

***Scheme 1.1.1*** Comparison of stabilities of varies olefin-metal complexes. For each pair of dienes, the left one is the Diene* and the right is the Diene shown in equiation above

As described above, almost all of olefin-metal complexes have been used as precursors of catalysts in asymmetric catalysis despite that some of them can be directly used in achiral reactions. As an example, $[IrCl(COD)]_2$ can serve as a catalyst for arylation of ketones and imines, where the only ligand is the diene COD [29].

Some very stable complexes, such as ferrocene, have been intensively used as scaffolds to prepare chiral or achiral ligands based on phosphorus or nitrogen, which can be combined with another transition metals [30]-[31].

Before chiral olefins were prepared as ligands, the phosphine, nitrogen and a few sulfur based ligands [32, 33], [34] had already shown excellent performance in asymmetric catalysis. The reason that chiral olefins were not used in asymmetric catalysis previously may be attributed to the common notion that coordination of olefin ligands to metals is general more labile than other pnictogen based ligands.

Early studies were reported by Suemune and co-workers during 2000-2003 [35]-[36]. A series of chiral dienes were synthesized and their capability for coordination to a variety of metals was examined (compounds **18-21**, ***Scheme 1.1.2***). It was found that during the formation of compound **18** exclusive racemization occurred to the ligand **22**. This was confirmed by liberating **22** with triphenylphoshpine and re-checking the optical purity. Despite the enantiomeric purity of the ligand **22** being significantly reduced, complex **18** was tested as a catalyst for silylformylation of benzaldehyde **23a** [35]. It did not afford the desired product **24**, but the desilylated compound **25** in low yield. It is noteworthy that, although the reaction was not successful, it may be the first attempt to use a chiral olefin ligands for asymmetric catalysis [37]. Another example of a chiral diene-metal complex was reported by Panunzi and co-workers [38]-[39], in which 1,3,5,7-tetramethyl-2,6,9-trioxabicylco[3.3.1]nona-3,7-diene (tond) and its complex with Rh were synthesized and resolved with (*S*)-phenylethylamine to give {Rh[(1*R*, 5*R*)-tond][ (*S*)-phenylethylamine]Cl}(compound **21**, ***Scheme1.1.2***).



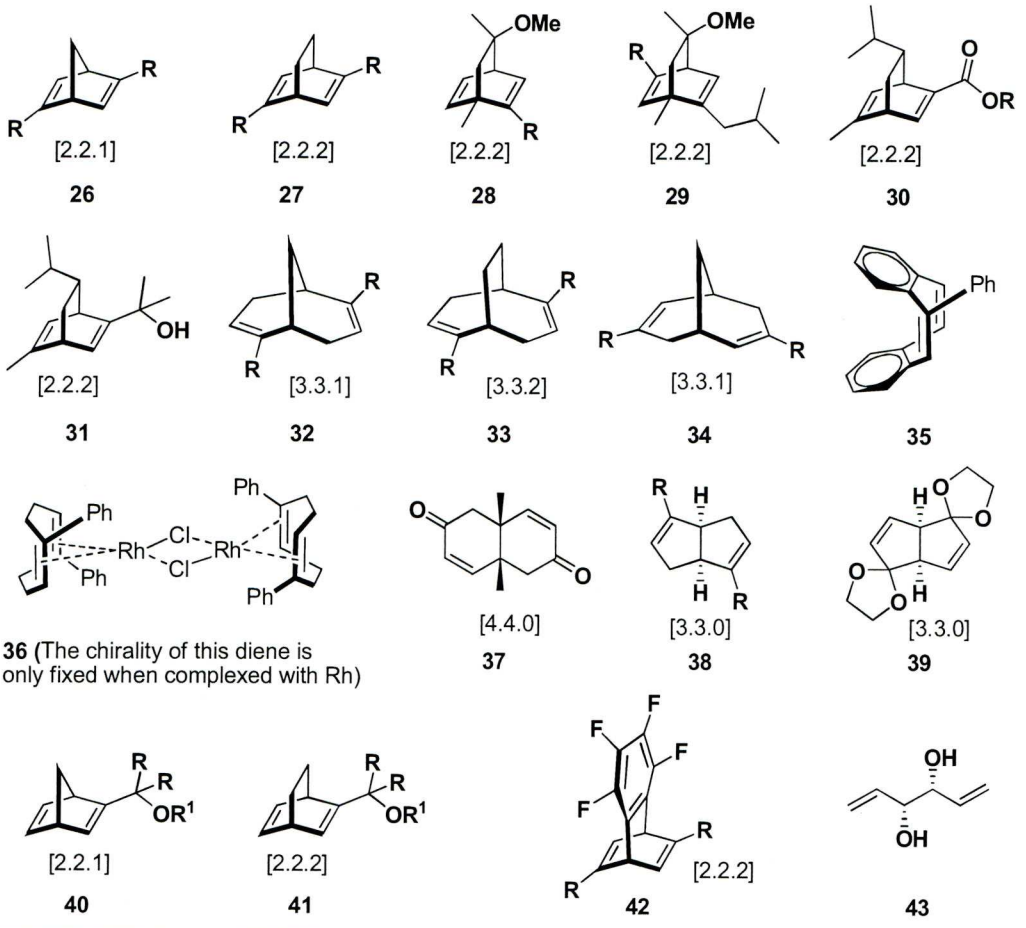

***Scheme 1.1.2*** Complexes of chiral dienes with transition metals and preliminary application in catalysis

## 1.2 Synthesis of Chiral Dienes

The successful application of a chiral diene as a ligand in asymmetric catalysis was not realized until the first example was reported by the Hayashi group in 2003 [40]. Shortly afterwards, Carriera also reported another chiral diene ligand and its application in kinetic resolution of allylic carbonates [41]. Since then, a series of chiral diene ligands have been synthesized and introduced into a variety of asymmetric catalytic reactions. A summary of scaffolds which have been made and

this is shown in ***Table 1.2.1***.

***Table 1.2.1*** Chiral diene ligands reported before 2010

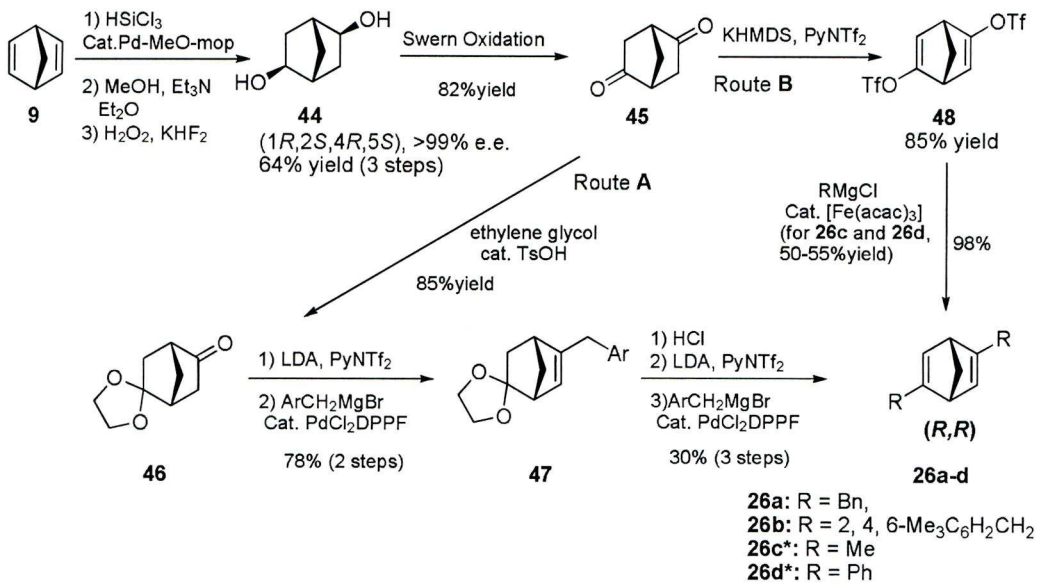



For the purpose of clarity, those scaffolds listed above are introduced according the synthetic methods used to construct them rather than in chronological order.

**(a) Asymmetic synthesis:**

Synthesis of **26** started with the cheap commercially available norbornadiene **9**. The norbornadiene underwent Pd-(*R*)-MeO-MOP-catalyzed asymmetric hydrosilylation [42] followed by Tamo-Fleming oxidation to give (1*R*, 4*R*)-2,5-*exo*, *exo*-bicylco[2.2.1]hepta-2,5-diol **44** with >99%e.e. The resulting diol **44** was further

oxidized to (1*R*, 4*R*)-bicylco[2.2.1]hepta-2, 5-dione **45** by using Swern oxidation [43]. Initially the 2,5-substituent groups were introduced step-wise, one ketone group of the chiral diketone **45** was protected with ethylene glycol to give ketal-ketone **46** [40], the other was converted into an enol triflate by treatment with base and Comins reagent and followed by Pd-catalyzed cross-coupling with Gringard reagents to give **47**. Removal of the ketal in **47** and repetation of the same protocol gave **26a-b** (Route A).



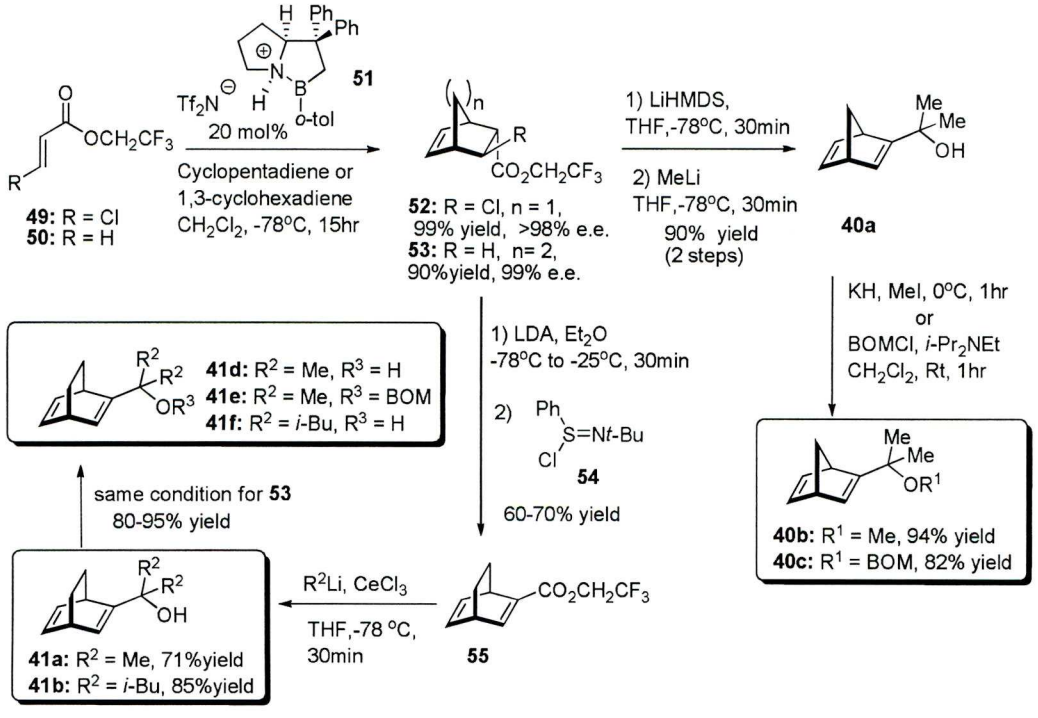

***Scheme 1.2.1*** Preparation of (*1,R,4R*)-2,5-disubstituted bicyclo[2.2.2]hepta-2,5-diene. ***26c** and **d** were not isolated but directly converted into rhodium complex due to their instabilities.

The sequential introduction of the substituent groups on the alkenes decreased the efficiency of the synthetic route. An optimized route (Route B in ***Scheme 1.2.1***) was reported later which enabled the simultaneous introduction of Bn, Me and Ph to give **26a, c** and **d** respectively [44].

Recently, Corey reported a method to construct chiral mono substituted bicyclic [2.2.1] and [2.2.2] diene ligands by using an asymmetric Diels-Alder reaction that was catalyzed by *N*-protonated oxazaborolidine **51** [45]. The synethetic route is shown in ***Scheme 1.2.2***. β-Chloro acrylate **49** reacts with cyclopentadiene in presence of **51** to

give the chiral bridged [2.2.1] product **52** in high yield and e.e. Following treatment with base to form the diene intermediate, the ester group was treated with 2eq. of MeLi to give product **40a** which was available to serve as a diene ligand. Diene ligand **40a** could be further modified by protecting the OH group with methyl or BOM to give chiral dienes **40b** and **40c**.

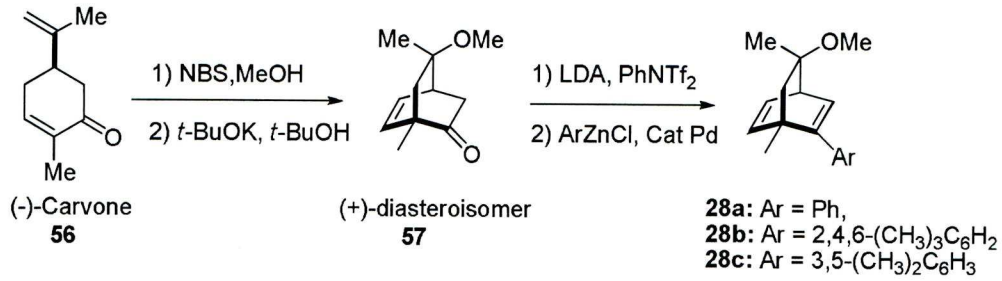
The synthesis of [2.2.2] system ligand **41** was only slightly different to that of **40** due to the different dienophile (**50**) used in the first step. The product of Diels-Alder reaction, **53**, was converted to chiral diene intermediate **55** by treatment with base followed by Mukaiyama reagent **54** [46]. Similarly, chiral mono substituted [2.2.2] diene ligands **41a-f** were synthesized by same methods used for **40**.




***Scheme 1.2.2*** preparation of mono substituted norbornadiene-based and bicylcooctadiene-based chiral dienes

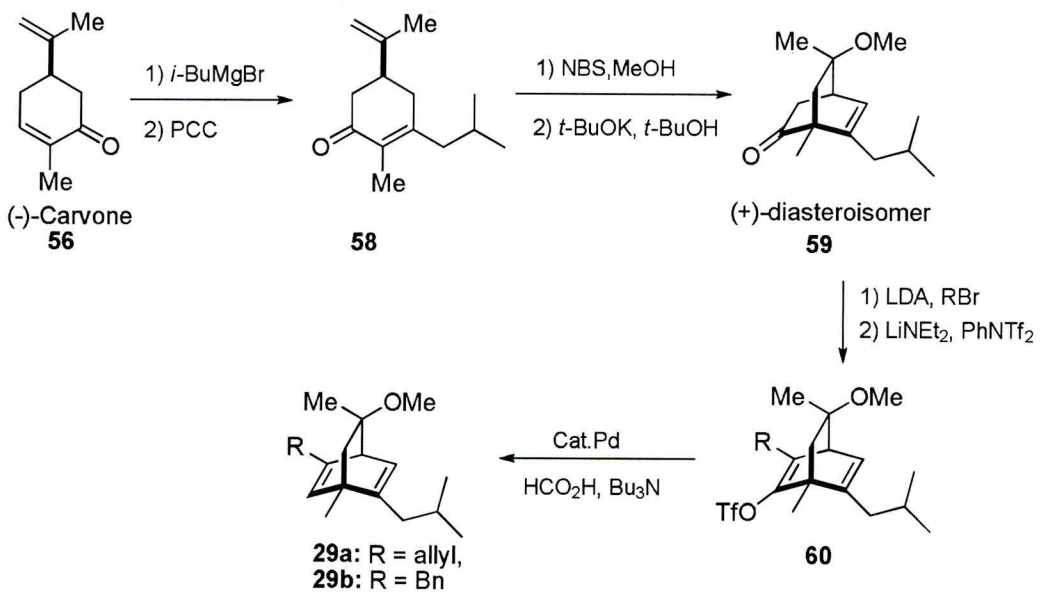
**(b) Chiral pool:**

In early 2004, Carriera reported another synthesis of chiral diene ligands which started using the cheap chiral natural product (-)-carvone (***Scheme 1.2.3***) [41]. Bromination of the electron richer terminal alkene in (-)-carvone **56** with NBS, trapping the brominium cation with methanol and subsequent enolization gave the bicyclic ketone **57**. This was treated with LDA and *N,N*-bis(trifluoromethylsulfonyl) aniline to form the corresponding vinyl triflate that can be converted into a range of aryl substituents to form **28**.



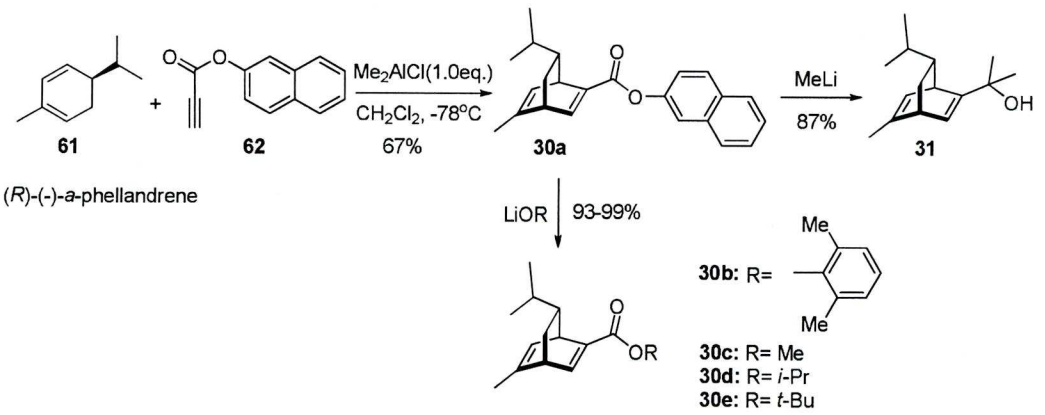

***Scheme 1.2.3*** Synthesis of the chiral mono substituted bicyclo[2.2.2]octadienes from (-)-Carvone

A second substituent could be introduced into this bicyclic scaffold by modifying the carvone at the beginning (***Scheme 1.2.4***) [47, 48]. Grignard addition to the carvone followed by PCC oxidation gave enone **58**, which was subjected to the same procedure described above to give diasteroisomer **59**. α-alkyation of the ketone in **59,** followed by enol triflation gave **60,** which underwent reductive detriflation to give the *pseudo-$C_2$* symmetric bicyclic chiral diene ligands **29a** and **29b**.



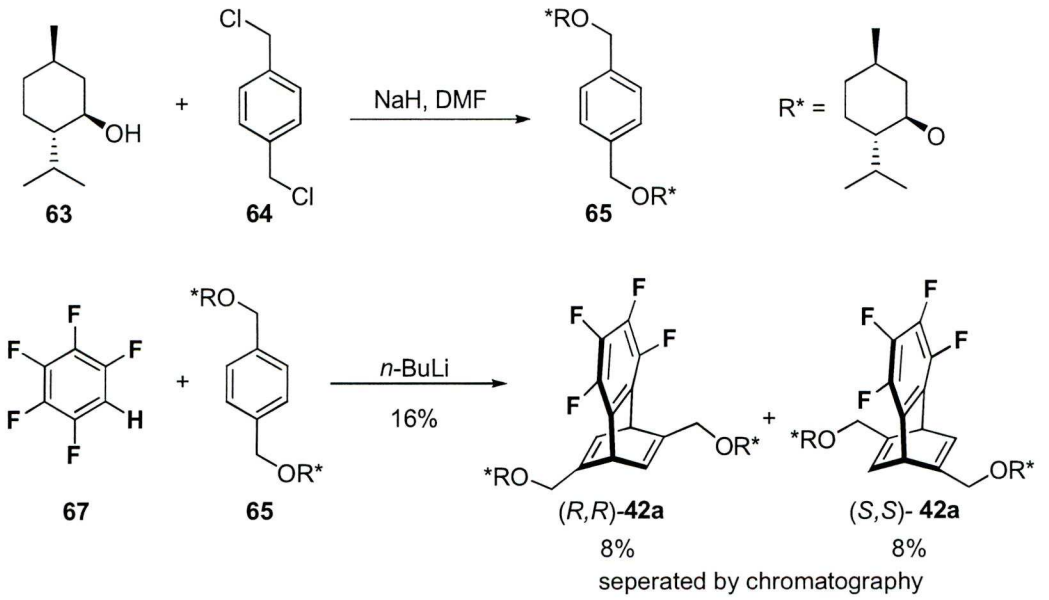

***Scheme 1.2.4*** Synthesis of the chiral disubstituted bicyclo[2.2.2]octadienes from (-)-Carvone

In order to increase the synthetic efficiency, a new [2.2.2] chiral diene scaffold was prepared by Hayashi group in 2008 and 2009 [49, 50], in which the chiral bridged diene compound was constructed using a substrate inducted asymmetric Diels-Alder reaction in one step (***Scheme 1.2.5***). By reacting (*R*)-(-)-α-phellandrene **61** with 2-naphthylpropiolate **62** in the presence of dimethylaluminium chloride, chiral diene **30a** was obtained with good yield and high e.e. Treatment of **30a** with *n*-BuLi gave the corresponding diene **31**. The napthyl ester in **30a** can also be converted to other ester groups by treatment with alkoxy lithium reagents (**30b-c**).



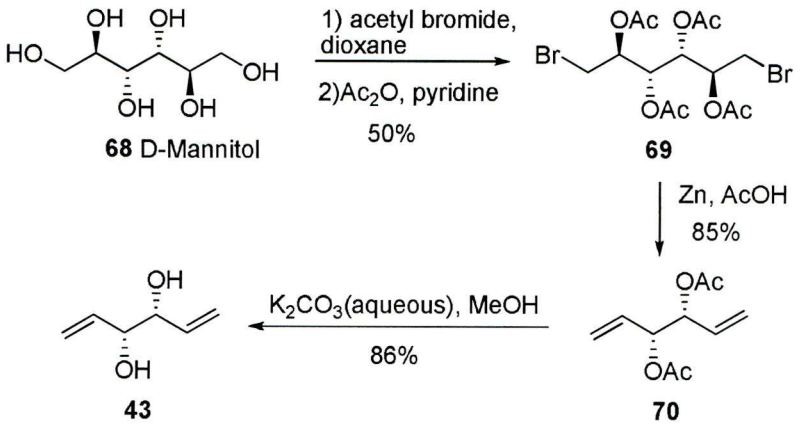

***Scheme1.2.5*** Preparation of (*R,R*)-bicyclo[2.2.2]octadiene from (*R*)-(-)-*a*-phellandrene

In 2008, another [2.2.2] based ligand system was reported by Hayashi group [51]. The diene **42** was constructed in an straightforward way: double etherification of L-menthol **63** with 1,4-bischloromethylbenzene **64** gave 1,4-dimenthoxymethylbenzene **65**, which was then followed by a [4+2] cycloaddition with tetrafluorobenzyne (generated from pentafluorobenzene **67** using *n*-butyllithium) to give the diastereoisomeric diene **42**. The chiral menthoxyl groups in the diene ligands enabled the diastereoisomers to be separated by silica gel chromatography. However the yield is remarkably low 8% for each isomer. In addition, although the introduction of the chiral menthoxy group brings the convenience for the separation of diastereoisomers, it also prevents the scaffold being modified further.




***Scheme 1.2-6*** Preparation of $C_2$-symmetric tetrafluorobarrelene ligands

Diene ligand **43** was the first acyclic chiral diene ligand applied in asymmetric catalysis [52]. The compound itself has been a widely used building block in synthetic chemistry [53-56]. There have been quite a few methods utilized to access this compound [53, 57] including the route shown in ***Scheme 1.2.7*** [58].

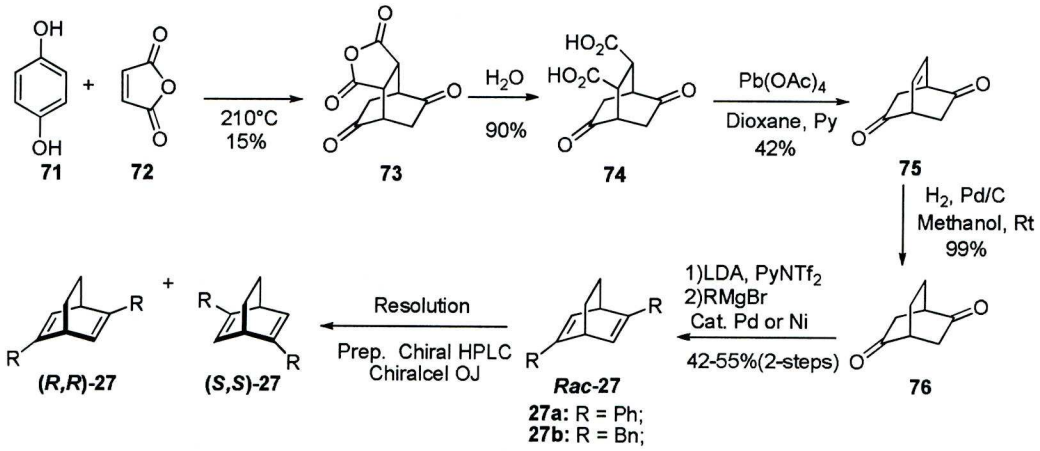



***Scheme 1.2.7*** Preparation of chiral diene ligand **40** from D-manntiol

Starting with D-mannitol **68**, via bromination of the terminal OH groups and acetylation of the remaining hydroxyl groups gave intermediate **69**, which then underwent elimination to give diene **70** in the presence of Zn in glacial acetic acid. Ligand **43** was obtained by hydrolysis of the acetyl groups in **70**.

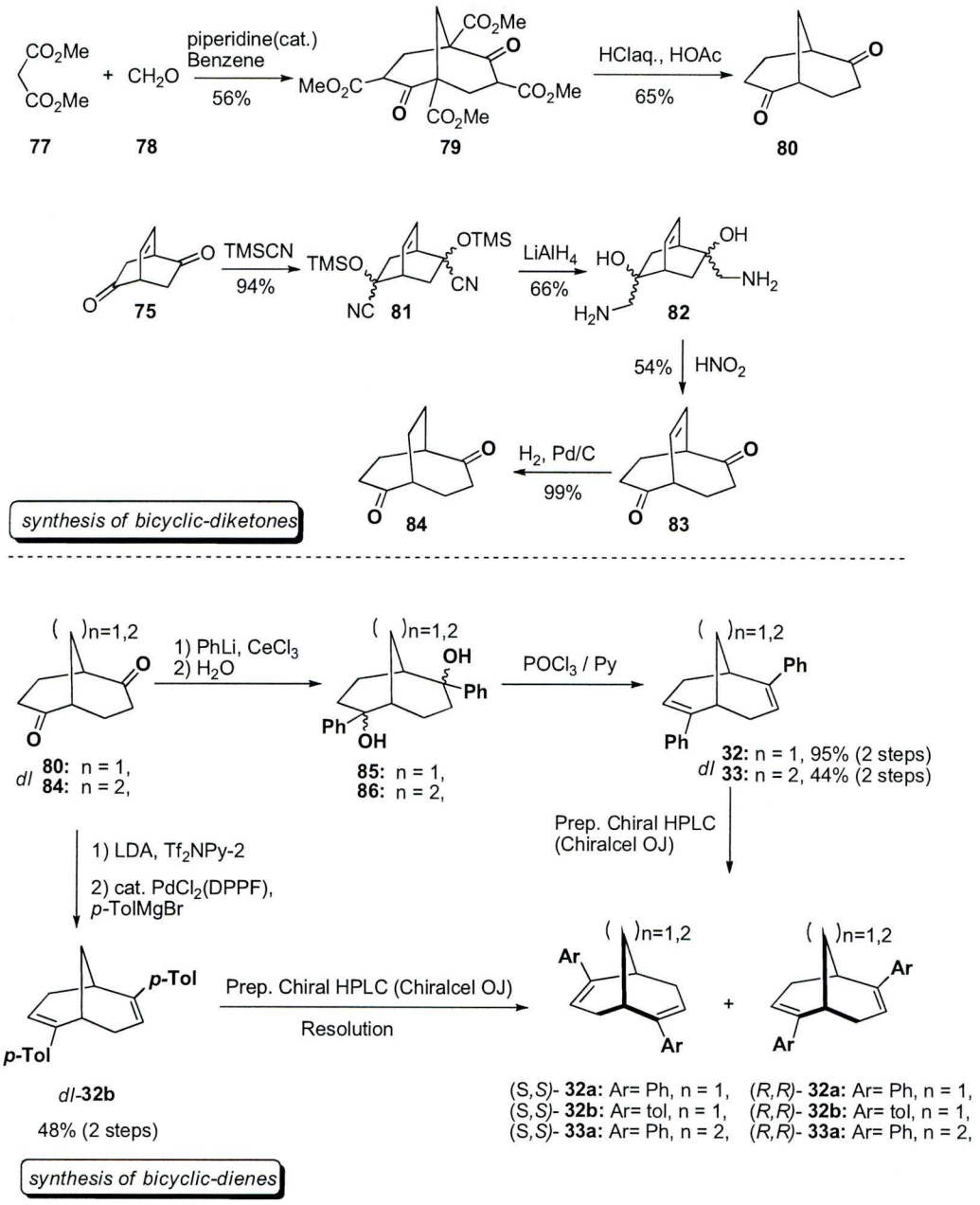
**(c) Chiral HPLC**

So far, of all the diene ligands that have been disclosed, those which require preparative HPLC to resolve either an intermediate or the final diene, possess a major position both in numbers and applications [18]. As shown in ***Scheme 1.2.8***, the $C_2$-symmetric bicylco[2.2.2]octadiene **27** reported by Hayashi group is perhaps the most widely used chiral diene ligand. The bridged structure **73** was formed by Diels-Alder reaction of hydroquinone **71** with maleic anhydride **72** in low yield. Hydrolysis of the anhydride moiety in **73** gave diacid **74**, which underwent oxidative decarboxylation, another low yielding step, to give compound **75**. Hydrogenation of the C=C bond gave **76**, which was converted into racemic diene ligands using a similar strategy described above to that for **26**. The chiral **27** was obtained *via* resolution on preparative chiral HPLC. It was notable that the total yield from starting material **71** and **72** to the rac-**76** was 5% and to rac-**27** was 2-3%, although the synthetic route is only 6 steps in total![59]




***Scheme 1.2.8*** Preparation of $C_2$ -symmetric 2,5-substituted-bicyclo[2.2.2]octa-2,5-diene

Hayashi and co-workers also prepared another two bicyclic scaffolds which needed to be resolved on chiral HPLC (***Scheme 1.2.9***).




***Scheme 1.2.9*** Synthesis of bicyclic [3.3.n] chiral diene ligands

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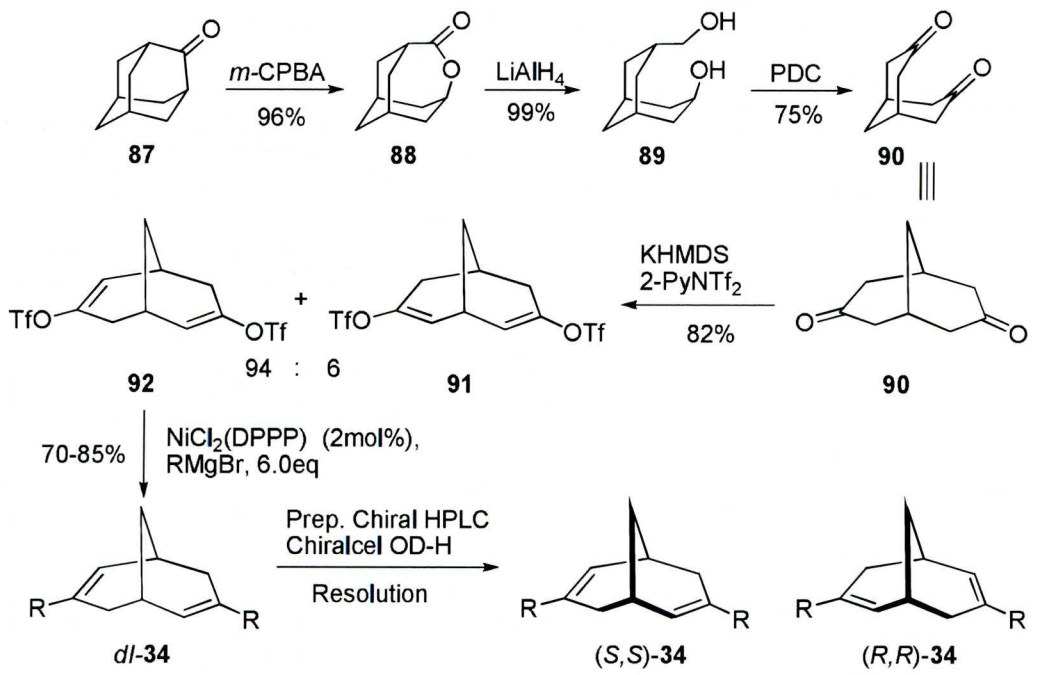
These bicyclic [3.3.n] (n=1 or 2) based chiral diene ligands were prepared via the same synthetic route except **33b** which was prepared by a similar method to that for **27** [60]. The *dl*-diketone **80** was prepared from methyl malonate **77** and formaldehyde **78** in 2 steps, which can be scaled up to over one hundred grams although the overall yield is not high [61-63]. The initial adduct

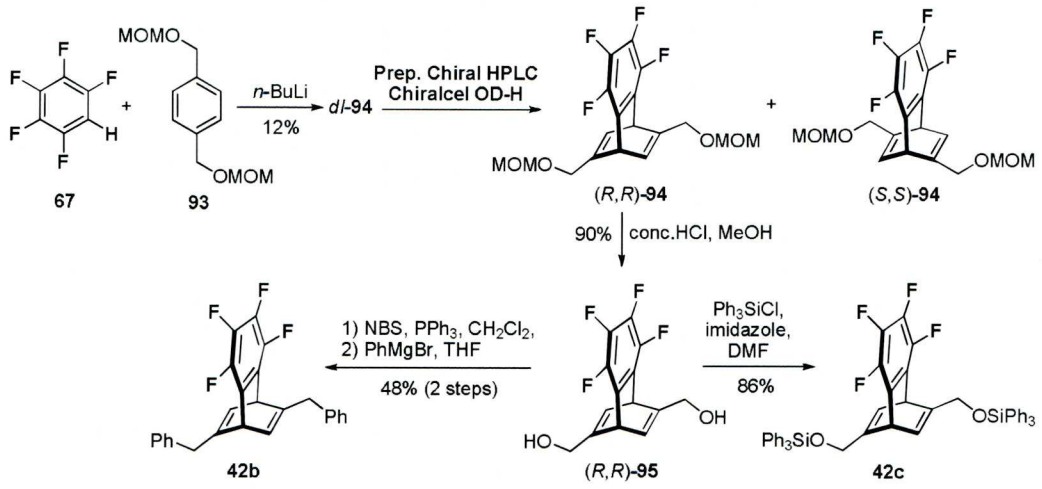
1,3,5,7-tetracarboxymethylbicylco[3.3.1]nonane-2,6-dione **79** was decarboxylated by treatment of HCl to give **80**. However, the *dl*-diketone **84** is more difficult to access due to the very low yielding route for **75** which was discussed previously [59]. By reacting trimethyl cyanide with **75**, TMS group protected cyanohydrin **81** was obtained in high yield. $LiAlH_4$ reduction of **81** gave **82** which underwent ring expansion by treatment with $HNO_2$ to give intermediate **83**. After hydrogenation of the C=C in **83**, the *dl*-diketone **84** was obtained smoothly. Lithium reagent addition to the *dl*-diketone **80** or **84** gave corresponding adducts (**85** and **86**), which were treated with trichlorophosphine oxide and refluxed in pyridine to give *dl*-**32** and **33**. The chiral diene ligands were obtained by resolution of *dl*-**32** and **33** on chiral preparative HPLC.

Another 3,7-disubstituted bicyclo[3.3.1] nonane based diene ligand system also reported by Hayashi and co-workers is shown in ***Scheme 1.2.10*** [64, 65]. The 3,7-disubstituted bicylo[3.3.1] nonane chiral dienes **34** can be prepared from bicylo[3.3.1]non-3,5-dione **90** *via* a similar route for the other dienes discussed above. Bicylo[3.3.1]non-3,5-dione **90** was prepared from commercially available 2-adamantanone **87** in three steps (***Scheme 1.2.10***). Bayer-Villager oxidation of **87** gave lactone **88** followed by $LiAlH_4$ reduction to give **89** with high yield. The bicylo[3.3.1]non-3,5-dione **90** was obtained in high yield by PDC (pyridinium dichromate) oxidation of **89**.



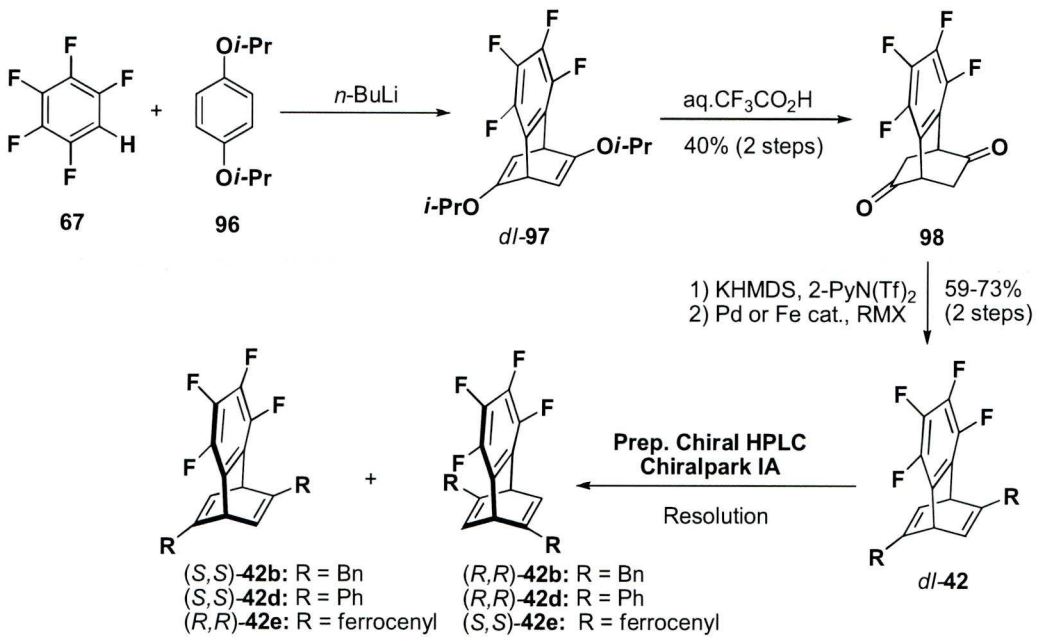

***Scheme 1.2.10*** Preparation of 3,7-substituted bicyclo[3.3.1] chiral dienes

In order to increase the modification of the chiral tetrafluorobenzobarrelene ligand **42** mentioned previously, the MOM group substituted compound **93** was utilized instead of menthoxy group [66]. *dl*-Barrelene-**94** was prepared according to the same procedure with similarly low yield. The single enantiomer **94** was obtained *via* resolution on chiral HPLC, which was then followed by acid hydrolysis for removal of the MOM group to give intermediate **95**, which can be modified *via* of the bis hydroxyl groups.




***Scheme 1.2.11*** Preparation of $C_2$-symmetric tetrafluorobarrelene ligands

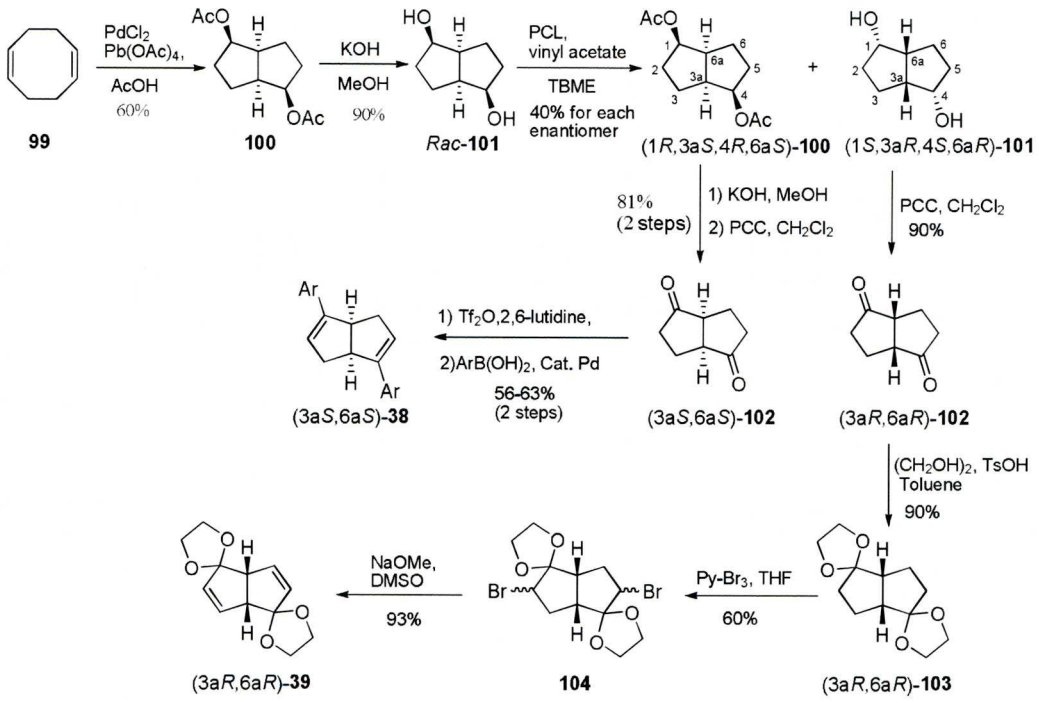
Most recently, an alternative synthetic strategy was applied to this tetrafluorobenzobarrelene scaffold [67], The diketone **98**, the common starting material of corresponding diene, was constructed by a [4+2] cycloaddition using 1,4-diisoproproxybenzene **96** reacting with tetrafluorobenzyne to give adduct **97**, which underwent acidic hydrolysis with a 40% overall yield. By treatment of diketone **98** with similar synthetic methods mentioned above, a series of chiral dienes (**42b, 42d** and **42e**) were prepared. It can be concluded that the new synthetic strategy is improved both for yield and for flexibility of modification, although the pure single enantiomer can only obtained by chiral HPLC resolution.




***Scheme 1.2.12*** Preparation of $C_2$-symmetric tetrafluorobarrelene ligands

**(d) Chemo-enzymatic method**

In 2007, a 2,5-substituted bicyclo[3.3.0]octadiene was disclosed by Laschat [68]and Lin[69] independently and prepared using very similar routes. This kind of diene ligand was based on compound **101**, which was first synthesized in 1934 and has been a widely used synthon in synthetic chemistry [54-57]. Due to the wide usage of **101**, efforts toward the resolution had been made and a successful kinetic resolution by lipase-catalyzed transfer-esterification has been established [70, 71]. As shown in ***Scheme1.13***, 1,5-cyclooctadiene underwent a trans-annular ring closure catalyzed by Pd in the presence of $Pb(OAc)_4$ and HOAc to give *Rac*-**100**, which was followed by hydrolysis. This was then subjected to enzyme resolution to give (1*R*,3a*S*,4*R*,6a*S*)-**100** and (1*S*,3a*R*,4*S*,6a*R*)-**101** with high yield and high enantioselectivity. Basic hydrolysis followed by oxidation gave enantiomerically pure bicylco[3.3.0]octa-2,6-dione **102**, which underwent enoltriflation and Suzuki coupling to give the desired chiral diene ligand **38**.

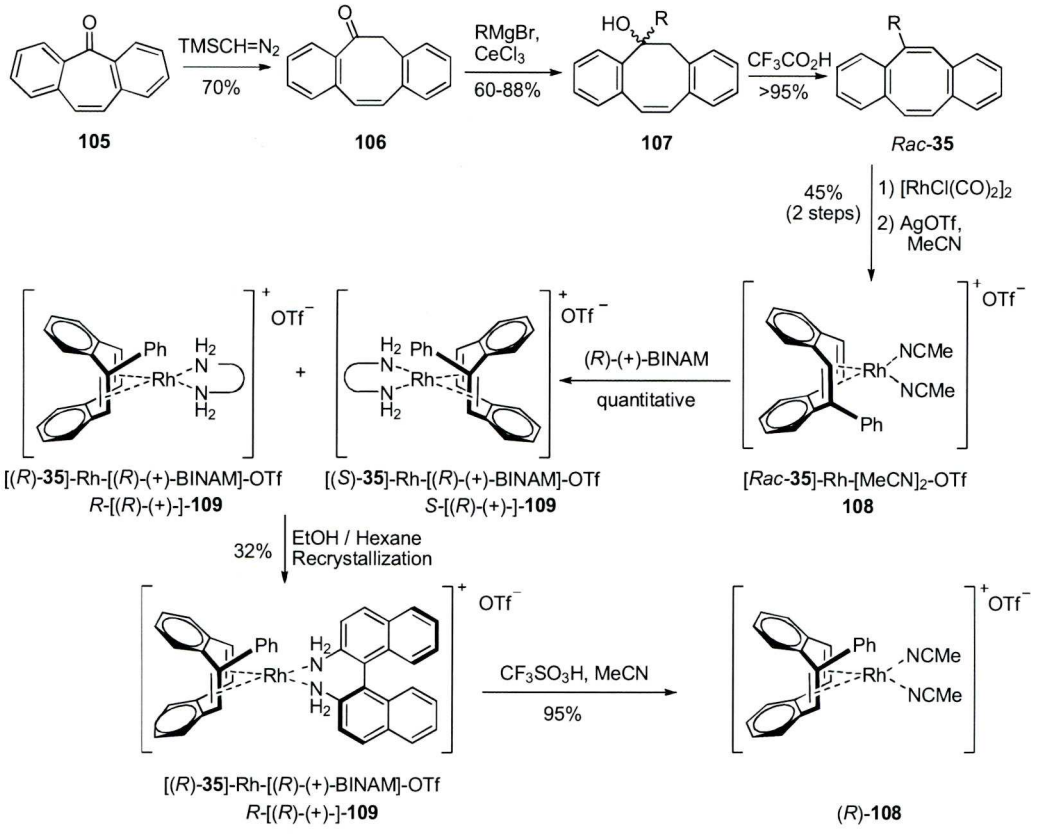



***Scheme 1.2.13*** Preparation of bicylco[3.3.0]octane chiral diene ligands

Another chiral diene ligand **39** which bears a 1,3-dioxarane moiety was prepared from enantiomerically pure **100** using a different strategy. The ketone groups in (3a*R*,6a*R*)-**102** underwent protection with ethylene glycol. Subsequent bromination by pyridine tribromide and elimination gave (3a*R*,6a*R*)-**39**, which was used as a hydrophilic ligand in asymmetric reactions using water as solvent [72].

**(e) Stoichiometric resolution by chiral metal complex:**

Gruzmecher and coworkers synthesized a $C_1$-symmetric chiral diene ligand **35** based on dibenzo[a,e]cyclooctenes [73]. The synthetic route is shown in ***Scheme 1.2.14***. Starting from dibenzosuberenone **105**, compound **106** was obtained *via* a ring expansion reaction in the presence of (trimethylsilyl)diazomethane. The reaction of **106** with phenylcerium reagent generated *in situ* from phenylmagnesium bromide and cerium trichloride produced **107** in good yield. Elimination of $H_2O$ in the presence of trifluoroacetic acid gave racemic **35** in high yield.

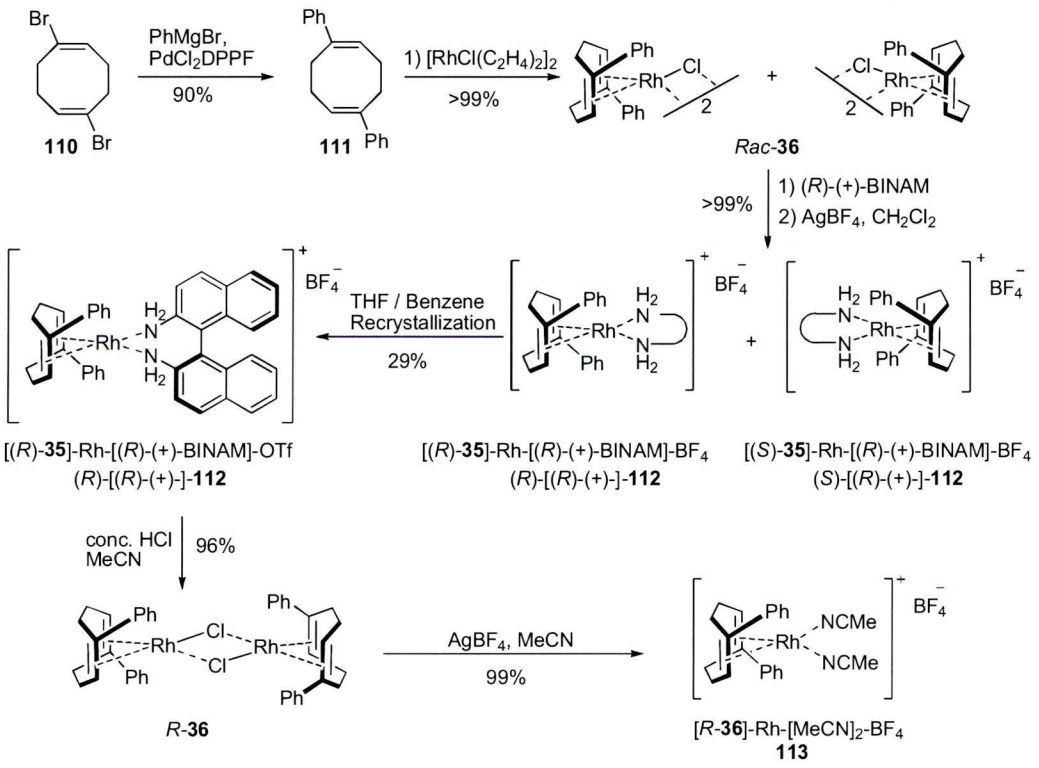



***Scheme 1.2.14*** Preparation of $C_1$-symmetric dibenzo[*a*,*e*]cyclooctene based chiral diene Rh-complex

The following resolution is based on the formation of a pair of diasteroisomers of the metal complex as shown in ***Scheme 1.2.14***. *Rac*-**35** was complexed with $[RhCl(CO)_2]_2$ followed by removal of the chloride by silver triflate to give the solvent coordinated Rh cation **108**. Displacing the coordinated solvent in **108** with (*R*)-(+)-BINAM gave (*R*)-[(*R*)-(+)-]-**109** and (*S*)-[(*R*)-(+)-]-**109** as a mixture, which could be purified to give enantiomerically pure (*R*)-[(*R*)-(+)-]-**109** by re-crystallization in hexane-ethanol mixed solvent in 32% yield. Efforts toward purification for the (*S*)-[(*R*)-(+)-]-**109** failed. The enantiomerically pure **108**, which can serve as a catalyst, was obtained from (*R*)-[(*R*)-(+)-]-**109** by treatment of triflic acid in acetonitrile.

The same concept was adapted by Hayashi and co-workers to resolve a rhodium

complex bearing a 1,5-diphenyl-1,5-cyclooctadiene **36** by the formation of diastereoisomers **113** [74]. However, this route also shared the same problem that only the one enantiomer (*R*-**36**) could be obtained as shown in the ***Scheme 1.2.15.*** Here, a different strategy was applied to *rac*-**36**, instead of adding silver salt to remove the chloride, the (*R*)-BINAM was added firstly to break the *rac*-**36** dimer and then followed by the addition of silver salts, which ensured a high yield to produce diastereoisomers **112**. The (*R*)-[(*R*)-(+)-]-**112** was able to be purified as an optically pure diastereoisomer, which was treated with concentrated HCl in MeCN to give enantiomerically pure (*R*)-**36**. Removal of the chloride by silver tetrafluoroborate in MeCN gave **113**: an alternative catalyst for asymmetric conjugate addition.

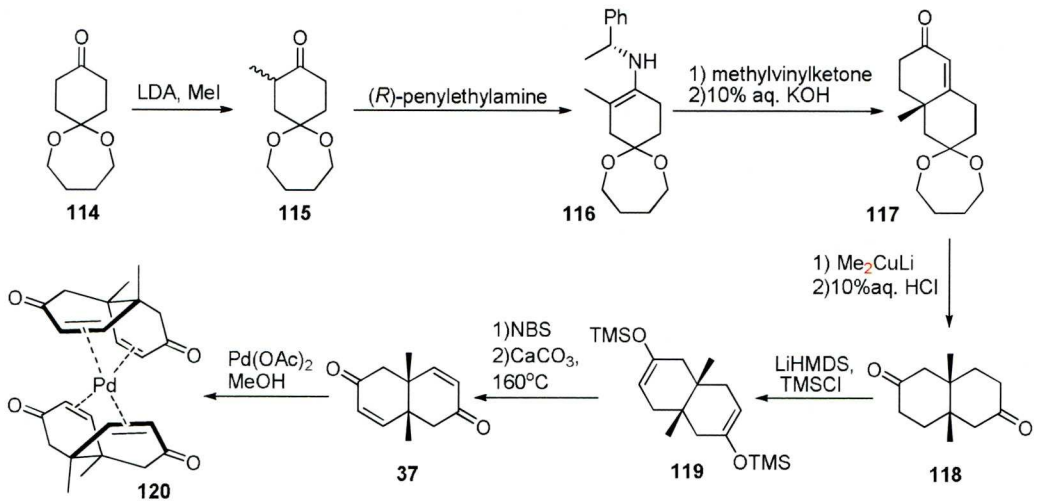



***Scheme 1.2.15*** Preparation of $C_1$-symmetric dibenzo[*a*,*e*]cyclooactene based chiral diene Rh-complex

**Chiral bis enone ligand for Pd(0):**

Inspired by the well-known coordination chemistry of $Pd_2(dba)_3$ **7**, and led by a molecular modeling study, bicyclic bis(enone) **37** was designed as a Pd(0) ligand [75].

The synthetic route is shown in scheme 1.2-16 [75, 76]. Starting from **114**, after methylation chiral enamine **116** was prepared and allowed to entio-selectively undergo Robinson annulation to give **117**, which underwent conjugate addition by treatment with lithium methylcuprate followed by hydrolysis of the acetal to give compound **118**. This was converted into its corresponding enolsilylether **119**, which underwent a bromination and dehydrobromination sequence to give the desired chiral diene ligand **37**, ready for the preparation of Pd catalyst **120**.



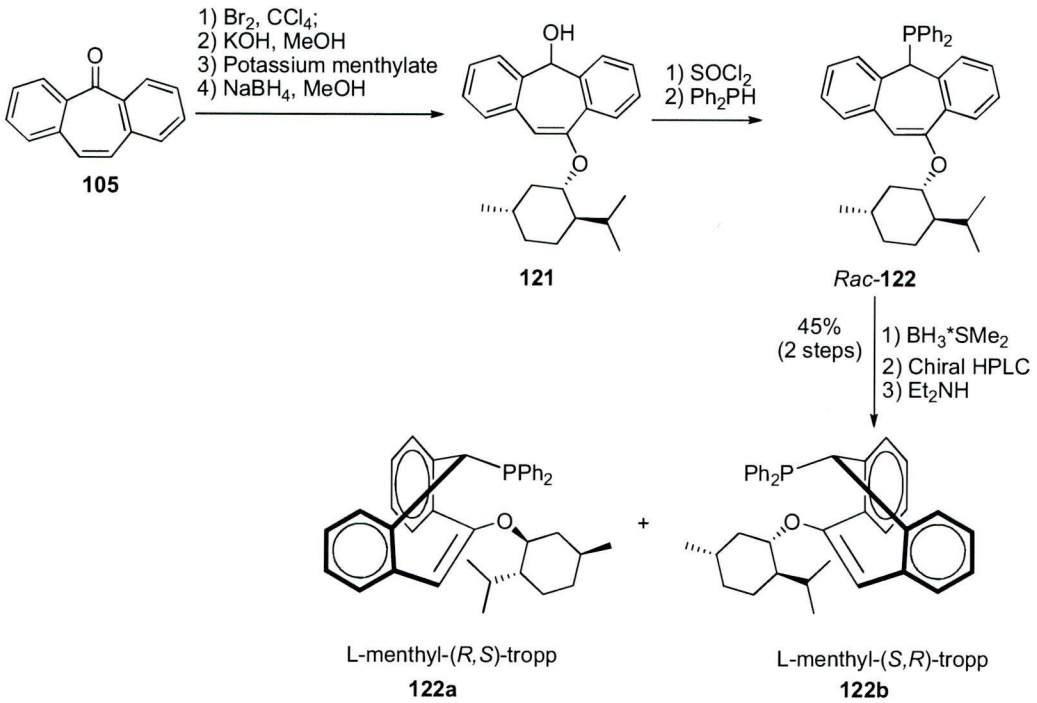

***Scheme 1.2.16*** Preparation of chrial bicycylic-bis(enone) diene

## 1.3 Chiral Pnicogen–Olefin Hydride Ligands

### Chiral Phosphino-Olefin ligand:

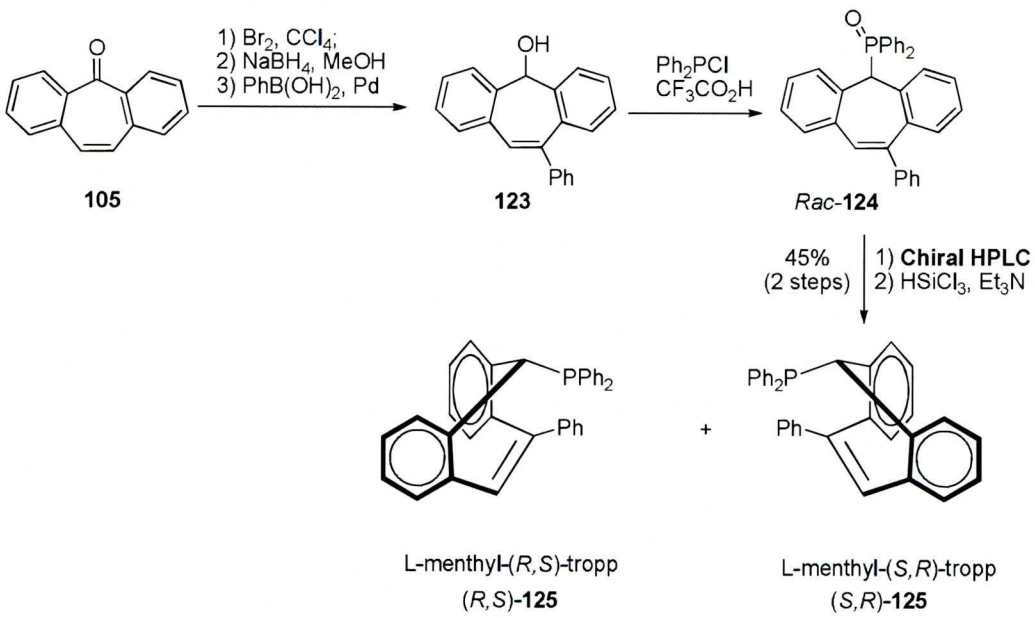
In 2005, Grützmacher and co-workers developed a series of phosphino-olefin hydride ligands for the purpose of asymmetric catalysis [77]. These types of ligands are especially interesting because they are topographically related to tripod ligands but serve only as four electron-donors whilst tripod ligands are usually six-electron donors. The ligand called $C_1$-tropp **122** was prepared from dibenzosuberenone **105**,

which underwent bromonation, dehydrobromonation, menthyloxy substitution and reduction of the ketone to give intermediate **121**. This allowed the conversion of the OH group into Cl by treatment of sulfonyl chloride, followed by nucleophilic attack by diphenylphosphine to give **122** as a mixture of 4 diastereoisomers. By borane protection, each isomer of **122** was able to be separated by preparative chiral HPLC and gave enantiomerically pure **122** after removal of the borane protection.



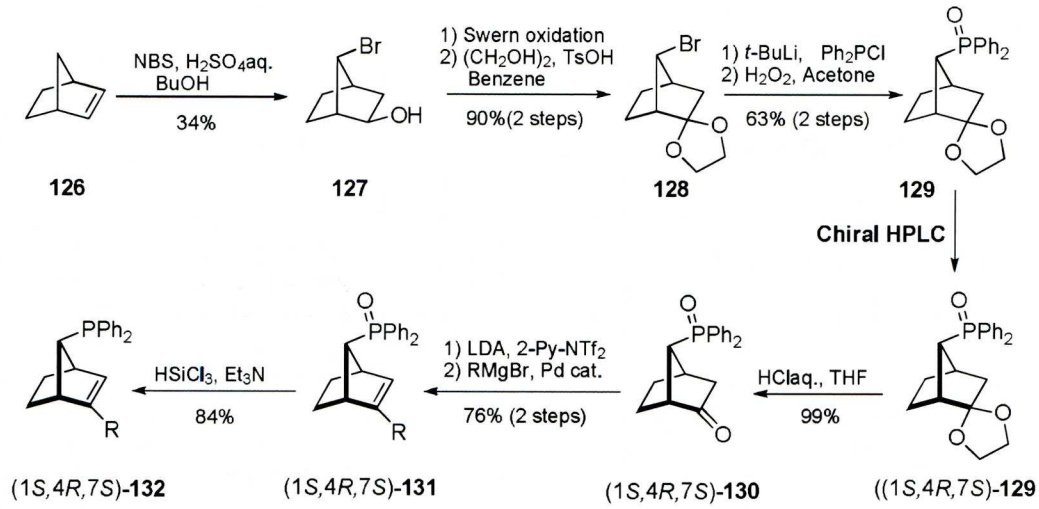

***Scheme 1.3.1*** Preparation of L-menthyl-(*R,S*)-tropp phosphino-olefin ligands

Another phosphane alkene chiral ligand was developed using the same idea. The ligand called $^{Ph}$tropp was synthesized as shown in in ***Scheme 1.3.2*** [78]. Still starting from dibenzosuberenone **105**, by a similar route intermediate **123** was synthesized with a phenyl being introduced to the olefin. Alcohol **123** underwent an Arbuzov reaction to give phosphine oxide **124,** as a pair of racemates which was separated by preparative HPLC to give pure enantiomers. Trichlorosilane reduction gave (*R,S*)-**125** or (*S,R*)-**125** respectively.



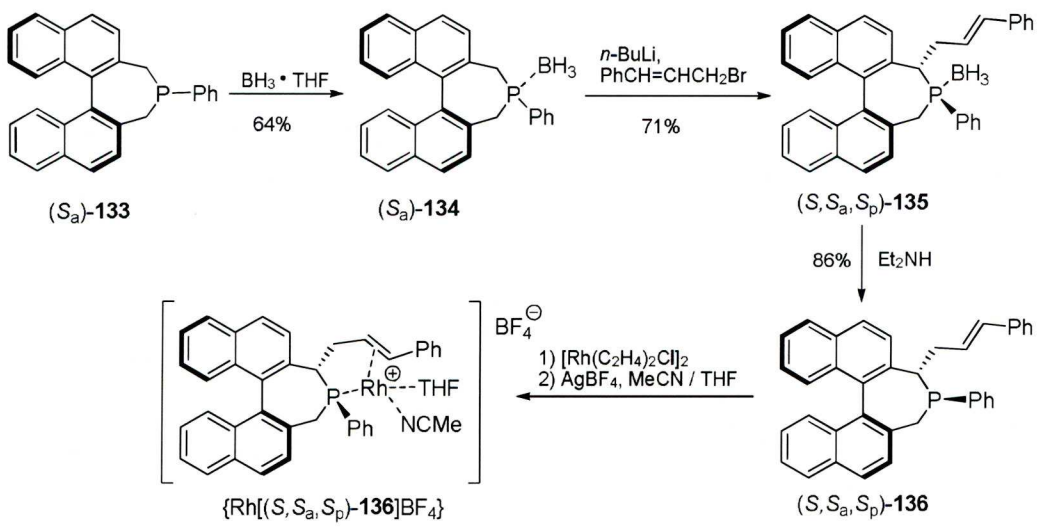

***Scheme 1.3.2*** Preparation of L-menthyl-(*R,S*)-tropp phosphino-olefin ligands

A chiral phosphino-olefin based on norbornene was reported by Hayashi [79, 80]. Treatment of norbornene **126** with hypobromous acid gave the highly regioselective addition product **127** but in a low yield [81]. Oxidation and ketal formation gave intermediate **128** in high yield. The bromo goup was transformed to give diphenylphosphino substituted compound **129** by lithiation of **128** followed addition of diphenylphosphine chloride and then oxidized with hydrogen peroxide. Enantiomerically pure **129** was obtained by chiral HPLC resolution and then undergone deketalization, enoltriflation, cross-coupling and reduction reaction sequences to give **132**.




***Scheme 1.3.3*** Preparation of chiral phosphino-olefin ligand based on the norbornane skeleton

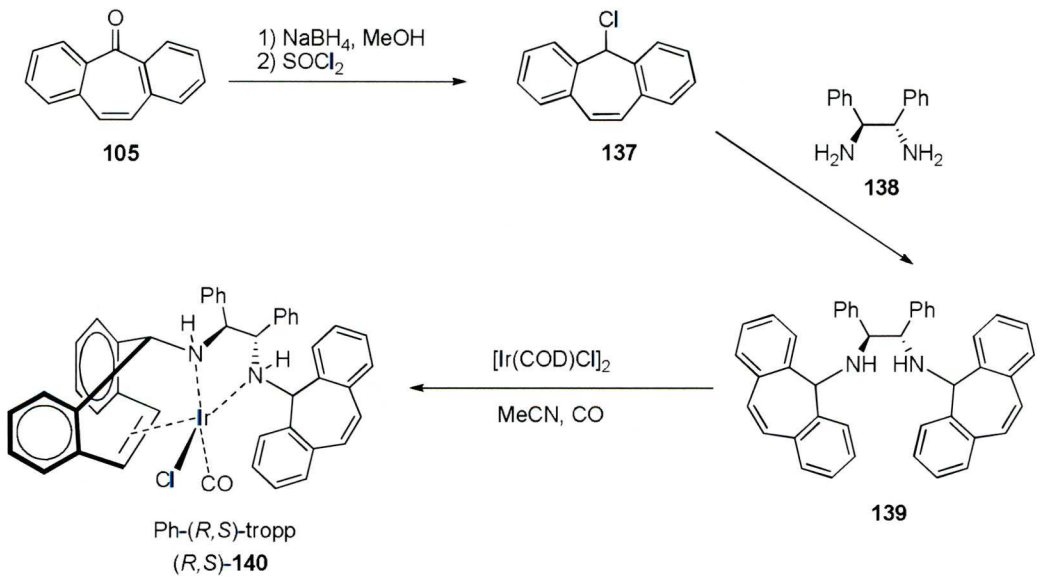
A phosphino-olefin ligand which has a relatively shorter synthetic route is shown in ***Scheme 1.3.4*** [82]. Starting from (*S*)-dinapthophosphepine **133**, a highly enantio-selective alkylation was realized by protection of phosphine in **133** with borane followed by lithiation and then addition of vinylbromide, by which **135** was obtained in moderate yield. Removal of borane protecting group by $Et_2NH$ gave the desired ligand **136**, which can coordinate with rhodium to form an active catalyst.




***Scheme 1.3.4*** Chiral phoshino-olefin ligand based on dinaphthophosphepine

**Chiral Amino-Olefin ligand:**

Unlike the phosphines, nitrogen based ligands, especially the tertiary amine serve predominantly as a pure donating ligands and with very little back-donation from the metal [18]. So theoretically, if there is a nigroen based ligand co-existing with an olefin ligand, the nitrogen ligand would strengthen the metal-olefin coordination bond compared with the phosphine which may weaken that coordination because of the strong metal-phosphine back-donation. From this perspective, it was very interesting to develop some amino-olefin hybrid ligands and study their application in asymmetric catalysis.

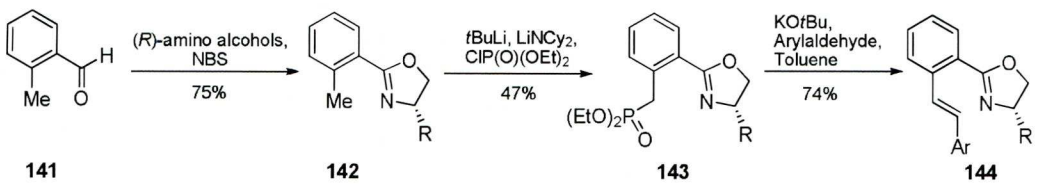



***Scheme 1.3.5*** Preparation of chiral tropp amino-olefin ligands

Grützmacher's group reported a concise synthetic route to prepare a diamine-diene ligand shown in ***Scheme 1.3.5*** [83]. Here again the dibenzosuberene was used as the alkene scaffold. Dibenzosuberenone **105** was converted into chlorinated compound

**137** by reduction of ketone into alcohol and followed by treatment with $SOCl_2$. Nucleophilic replacement of the chloro group by chiral amine **138** gave the desired nitrogen-olefin ligand **139**, which could form the Ir complex **140**.

Most recently, the Glorius group reported an olefin-oxazoline ligands which was called OlefOx **144** [84]. A clever synthetic strategy was designed to allow the final ligand to be highly modified in a few steps and to the avoid resolution as shown in ***Scheme 1.3.6***.




***Scheme 1.3-6*** Synthesis of Olefin-Oxazoline (OlefOx) ligands.

Starting from the *o*-methylbenzylaldehyde **141**, the aldehyde group was used to form the oxazoline moiety by reaction with an aminoalcohol followed by treatment with NBS to form **142**. Deprotonation of the methyl group in **142** followed by addition of diethyl chlorophosphate gave the corresponding phosphinate **143**, which was subjected to Horner-Emmons reaction to give the target ligand **144**.

## 1.4 Applications of chiral olefin ligands

There is no doubt that asymmetric catalysis has been the most important issue in organic chemistry in the past several decades. Quite a few protocols have been successfully transferred to industrial production (see ***Table 1.4.1***) [85].

***Table 1.4.1*** Transition metal catalyzed asymmetric reactions in industrial

| Product | Reaction and catalyst | Scale | Company |
|---|---|---|---|
| L-Menthol | Isomerization of allyl amine with Rh-binap | > 1000 t / y | Takasago |
| Vitamin E | Hydrogenation of allyl alcohol with Ru-binap | kilo-tons | Takasago |
| Glycidol | Sharpless epoxidation with Os-cinchona | multi t / y | PPG-Sipsy |
| Orlistat | Hydrogenation of β-keto ester with Ru-biphep or Raney-Ni-tartrate | multi t | Roche |

Development new asymmetric transformations with high reactivity and enantioselectivity is still a hot area due to the demand of quick access to vast amount of chiral compounds to fit the needs of industry especially from the pharmaceutical industry [86-88] (***Table 1.4-2***).

***Table 1.4.2*** Marketing data for chiral drugs

| | Global sales | | | |
|---|---|---|---|---|
| Year | 1998 | 1999 | 2000 | 2008 |
| TOTAL $ Millions | $99,389 | $115,001 | $146,013 | $180,000 |

Source: Technology Catalysts International Corp.

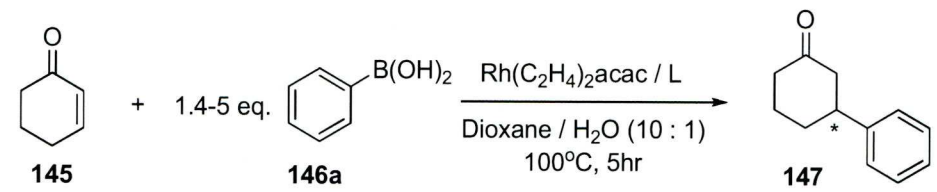
In the following section we will focus on the asymmetric reactions which have been realized using the chiral diene–rhodium complexes. These will be described according to reaction type.

**Asymmetric Conjugate Addition (ACA)**

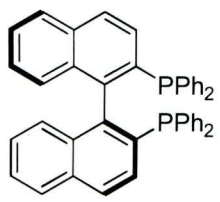
The most successful and impressive transformation using a chiral diene metal catalyst may be the asymmetric conjugate addition to activated olefins bearing electron-withdrawing functional groups such as ketones, aldehydes and amides, with aryl or alkenyl boronic acids.

The stereoselective conjugate addition of carbon nucleophiles to activated C=C bonds is one of the most important methods for the preparation of optically active natural products, pharmaceuticals and other specialty chemicals. Methodologies to achieve this transformation have been well-documented [89-94]. Here we focus on transition metal catalyzed asymmetric reactions using Rh-diene complexes.

The first example of a Rh-catalyzed ACA reaction of aryl or alkenyl boronic acids to activated alkenes was reported by Hayashi and Miyaura using chiral BINAP in 1998 [95]. Of all the chiral phophine ligands, BINAP was proved to be the most successful ligand. Other phosphine ligands gave significantly lower enantioselectivity than BINAP (***Scheme 1.4.1***) [89, 92, 93]. Although the Rh-BINAP system achieved excellent yield and e.e. in this reaction, there were still several factors which need to be improved. For example, the reaction temperature was generally over 100°C, which would consume excessive energy and accelerate hydrolysis of Rh-Aryl species, the side reaction that leading to consumption of multiple equivalents of aryl boronic acid.

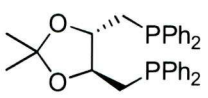



**145** **146a** **147**



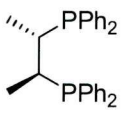

(*S*)-BINAP **148**

yield: 99%
e.e. : 97%



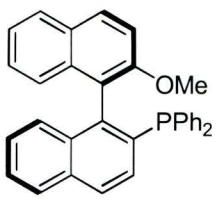

(*S,S*)-diop **149**

yield: 30%
e.e. : 24%



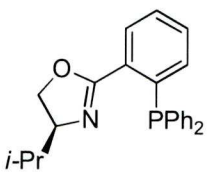

(*S,S*)-chiralphos **150**

yield: 72%
e.e. : 40%



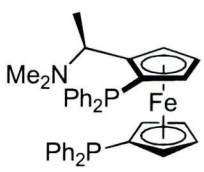

(*R*)-Meo-mop **151**

yield: <2%




(*S*)-*ip*-phox **152**

yield: 5%
e.e. : 0%



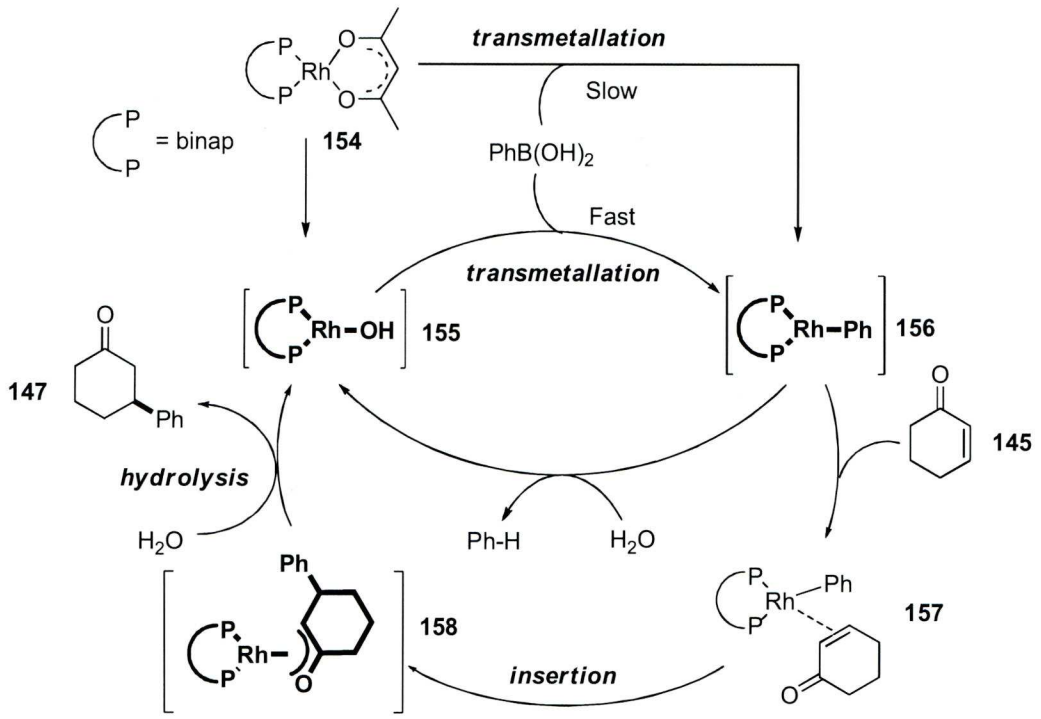

(*S*)-(*R*)-bppfa **153**

yield: 5%
e.e. : 3%

***Scheme 1.4.1*** Asymmetric conjugate 1,4-addition to 2-cyclohexenone by phosphine ligands

**Mechanism of the ACA reactions**:

With the help of NMR, the key intermediates were observed in the rhodium-catalyzed 1,4-conjugate addition of benzene boronic acid to 2-cyclohexenone [96]. The mechanism is shown in ***Scheme 1.4.2***.



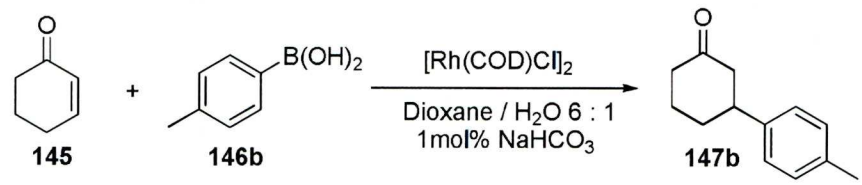

***Scheme 1.4.2*** Mechanism of Rh-catalyzed 1,4-conjugate addition

The reaction proceeds through several intermediates: hydroxorhodium species **155**, phenylrhodium **156** and oxa-π-allylrhodium **158** (drawn in bold), all of which have been observed in NMR studies. So the reaction cycle can be summarized as follows: transmetallation of hydroxorhodium complex **155** with phenylboronic acid gives phenylrhodium **156**, followed by the insertion of 2-cyclohexenone to form the oxa-π-allylrhodium species **158**. Upon hydrolysis of oxa-π-allylrhodium, the addition product is released and at the same time the active Rh catalyst hydroxohodium **155** is re-generated. It should be noted that a significant side reaction exists: the hydrolysis of phenylrhodium **156**, which could generate the active catalyst hydroxohodium species **155** but also afford benzene at same time [91]. As a result, this side reaction will lead to consumption of multiple equivalents of organo boronic acids.

It has turned out that the chiral dienes are more ideally suited to this kind of

transformation [97]. Pioneering works was carried out by Miyaura and co-workers. In 2001, they found that [Rh(COD)Cl] could serve as a highly active catalyst for conjugate addition of phenylboronic acid to α, β–unsaturated carbonyl compounds [98]. After screening of the reaction conditions, a large acceleration of reaction rate was found when using dioxane / water as solvent and a catalytic amount of $NaHCO_3$ as base. From ***Table 1.4.3*** it can be found that under the best conditions, with as little as 0.0002mol% rhodium catalyst (S : C = 500000 : 1), the 1,4-addition product **147b** could be isolated in 75% yield after 36 hrs. (***Table 1.4.3***, entry 6)

***Table 1.4.3*** The TON (tourn over number) of the $[Rh(COD)Cl]_2$




**145** **146b** **147b**

| Entry | Cat. Loaded (mol%) | Temperature / °C | Time / hr | yield (%) | TON |
|---|---|---|---|---|---|
| 1 | 0.01 | 90 | 16 | 98 | 9800 |
| 2 | 0.005 | 90 | 24 | 67 | 13400 |
| 3 | 0.005 | 90 | 36 | 97 | 18400 |
| 4 | 0.001 | 100 | 36 | 97 | 97000 |
| 5 | 0.0005 | 100 | 36 | 96 | 192000 |
| 6 | 0.0002 | 100 | 36 | 75 | 375000 |

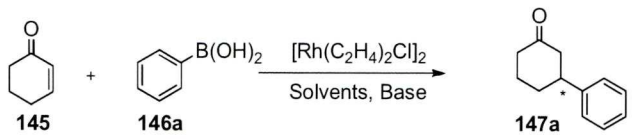
These results inspired chemists to develop an asymmetric protocol for this reaction by using chiral diene ligands. The first application of a chiral diene ligand in this transformation was reported by the Hayashi group in 2003, where chiral diene ligand **26** was shown to impact both high reactivity and enantioselectivity [40]. Since then, a variety of chiral bicyclic diene scaffolds, as well as phosphino-olefin and amino-olefin hybrids, have been successfully applied in this reaction. From the results Miyaura obtained (***Table 1.4.3***), the reactivity of Rh / chiral olefin complexes were expected to be very high as well. Still, an activity test of the Rh-**27** catalyst was

carried out by Hayashi, and it was found that with only 0.005mol% Rh-**27**, 71% isolated yield was obtained with a TOF of 14200$h^{-1}$. Moreover, it was important to note that the high enantioselectivity was maintained with such a low catalyst loading [99].

By comparing the catalytic performances between [Rh(COD)OH] and [Rh(binap)OH], it was found that the former showed much higher activity than the later. The reason behind this is that [Rh(COD)OH] has a much larger rate constant than [Rh(binap)OH] for the rate-determining transmetalation step[100].

***Table 1.4.4*** gives a summary for the results of activity and enantioselectivity for the pure chiral olefin ligands or olefin containing hybrid ligands recently achieved for the conjugate addition of 2-cyclohexene with benzene boronic acid.

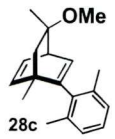
***Table 1.4.4*** Catalytic performacnes of pure diene ligands and olefin hybrid ligands



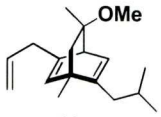

**145** **146a** **147a**

**26a**
Yield(%): = 94
e.e. (%): = 96

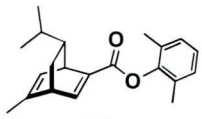
**27a**
Yield(%): = 97
e.e. (%): = 96



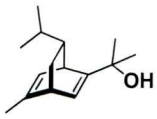
**28c**
Yield(%): = 99
e.e. (%): = 95



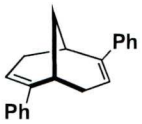
**29a**
Yield(%): = 87
e.e. (%): = 95



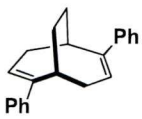
**30b**
Yield(%): = 96
e.e. (%): = 99



**31**
Yield(%): = 95
e.e. (%): = 99

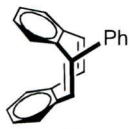


**32a**
Yield(%): = 93
e.e. (%): = 83

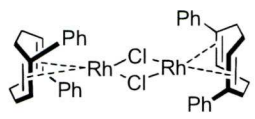


**33a**
Yield(%): = 98
e.e. (%): = 90

**34a:** Ar = 4-MeO-$C_6H_4$
Yield(%): = 91
e.e. (%): = 98

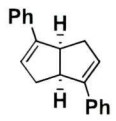


**35**
Yield(%): = 92
e.e. (%): = 62

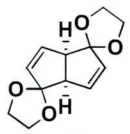


**36** (The chirality of this diene is only fixed when complexed with Rh)
Yield(%): = 89
e.e. (%): = 81

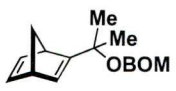
In the the reaction **36** was used, arylzinc chloride was used instread of boronic acid.



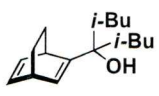
**38**
Yield(%): = 96
e.e. (%): = 91



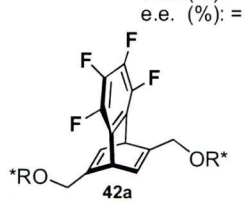
**39**
Yield(%): = 96
e.e. (%): = 93



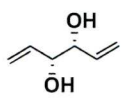
**40c**
Yield(%): = 95
e.e. (%): = 96



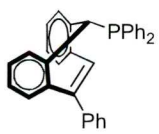
**41f**
Yield(%): = 98
e.e. (%): = 96



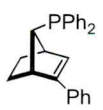
**42a**
Yield(%): = 94
e.e. (%): = 99



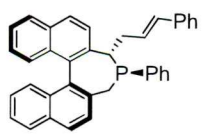
**43**
Yield(%): = 99
e.e. (%): = 83



(*R,S*)-**125**
Yield(%): = 85
e.e. (%): = 95



**132a**
Yield(%): = 94
e.e. (%): = 93



(*S,S*$_a$,*S*$_p$)-**136**
Yield(%): = 88
e.e. (%): = 98

**144** Ar = 2,3-di(MeO)-$C_6H_3$
Yield(%): = 94
e.e. (%): = 96

For each scaffold, only the best ligand is shown in this table. Except for the addition to the enones, varieties of α,β-unsaturated Michael acceptors were studied for this reaction.

The high enantioselectivity and chirality could be understood using the model shown

in ***Fig. 1.4.1***. The enantio-selectivity is decided by the hinderance difference given by the substitutents at the 2,5-positions and the hydrogen atoms at 3,6-positions [40, 101]. According to the model, the absolute configuration of the final products can also be predicted conveniently.

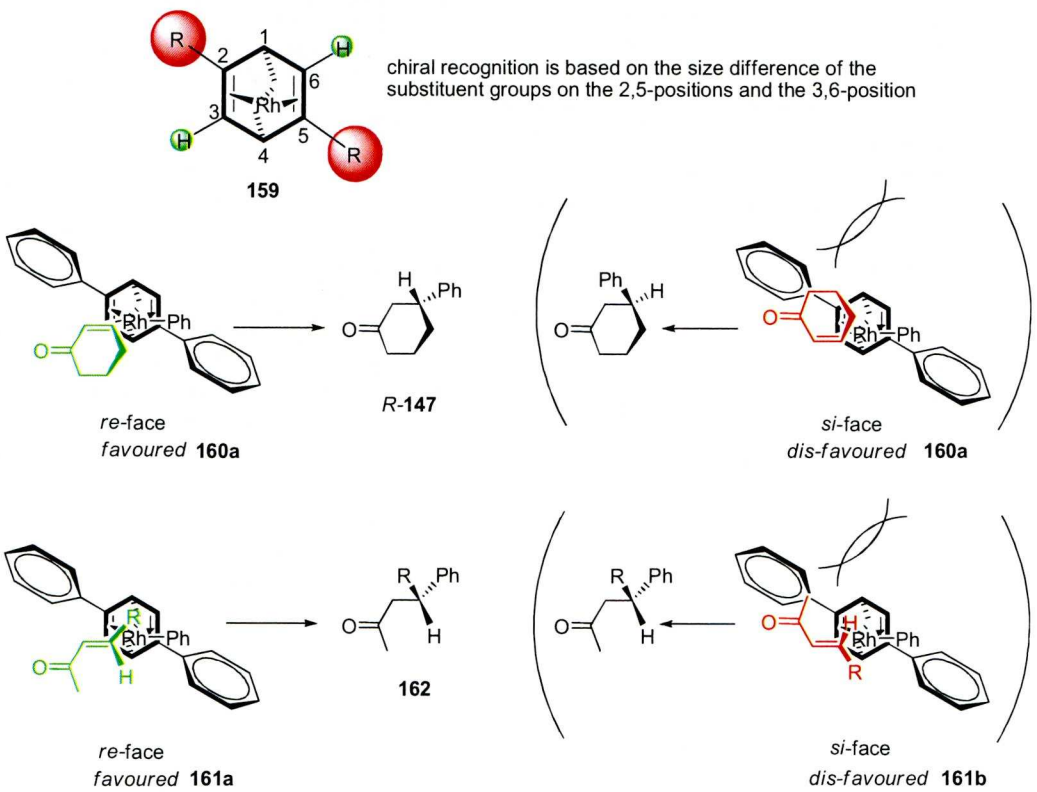
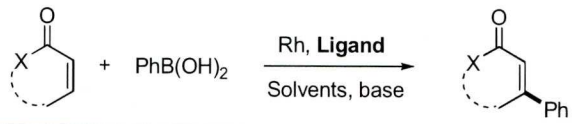


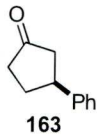

***Fig. 1.4.1*** chiral recognition model of chiral diene ligands

**Scope of products from the Rh-diene-catalyzed ACA reaction**:

A wide range of substrates have been tried with chiral olefin ligands, for example, the substrates include α,β-unsaturated ketones, aldehydes, amides and esters etc. and can be both cyclic and acyclic. The results again proved that olefin ligands are excellent ligands for this type of reaction. Almost all reactions were carried out at mild temperature, much lower than that required by phosphine ligands. Generally, a very high enantioselectivity and high yield could be achieved using this type of ligand (***Table 1.4.5***).

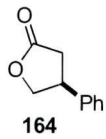
***Table 1.4.5*** Product scope from Rh-Olefin catalyzed conjugate addition



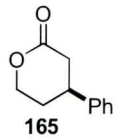
**163**

| Ligand | Yield | e.e.% |
|---|---|---|
| **26a** | 88 | 88 |
| **27a** | 97 | 99 |
| **28b** | 95 | 96 |
| **29a** | 91 | 94 |
| **32a** | 86 | 91 |
| **33a** | 98 | 84 |
| **34a** | 87 | 96 |
| **36** | 80 | 90 |
| **38** | 96 | 96 |
| **39** | 95 | 80 |
| **40c** | 95 | 97 |
| **41f** | 96 | 89 |
| **42a** | 99 | 94 |
| **43** | 87 | 61 |
| **132a** | 91 | 98 |
| **136** | 70 | 88 |
| **144** | 81 | 97 |



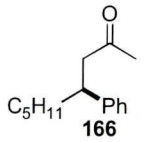
**164**

| Ligand | Yield | e.e.% |
|---|---|---|
| **29a** | 80 | 90 |
| **36** | 86 | 96 |



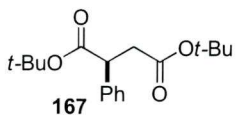
**165**

| Ligand | Yield | e.e.% |
|---|---|---|
| **26a** | 44 | 89 |
| **27a** | 75 | 95 |
| **36** | 99 | 98 |
| **38** | 87 | 93 |
| **39** | 85 | 80 |
| **43** | 84 | 62 |
| **132a** | 89 | 97 |
| **136** | 72 | 90 |



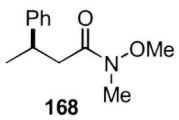
**166**

| Ligand | Yield | e.e.% |
|---|---|---|
| **27b** | 94 | 98 |
| **32** | 86 | 67 |
| **33** | 85 | 59 |
| **30b** | 97 | 98 |
| **31** | 95 | 99 |
| **41b** | 85 | 99 |
| **42a** | 85 | 99 |
| **127a** | 91 | 72 |
| **136** | 84 | 95 |



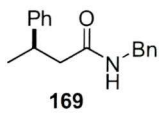
**167**

| Ligand | Yield | e.e.% |
|---|---|---|
| **26c** | 86 | 90 |



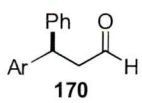
**168**

| Ligand | Yield | e.e.% |
|---|---|---|
| **27b** | 92 | 90 |



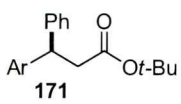
**169**

| Ligand | Yield | e.e.% |
|---|---|---|
| **27b** | 92 | 92 |



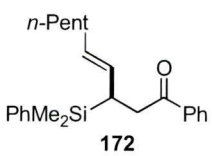
**170**

| Ligand | Yield | e.e.% |
|---|---|---|
| **27b** | 86 | 90 |
| **29b** | 70 | 92 |
| **42a** | 80 | 99 |



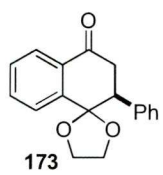
**171**

| Ligand | Yield | e.e.% |
|---|---|---|
| **29b** | 95 | 91 |
| **42a** | 97 | 98 |



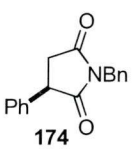
**172**

| Ligand | Yield | e.e.% |
|---|---|---|
| **26** | -- | 40- 52 |
| **27** | -- | 6-30 |
| **34** | 91 | 97 |



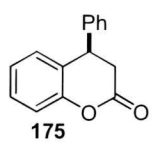
**173**

| Ligand | Yield | e.e.% |
|---|---|---|
| **27a** | 98 | 98 |



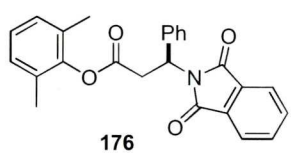
**174**

| Ligand | Yield | e.e.% |
|---|---|---|
| **26a** | 88 | 69 |
| **125** | 98 | 80 |
| **132a** | 98 | 93 |



**175**

| Ligand | Yield | e.e.% |
|---|---|---|
| **29a** | 43 | 98 |



**176**

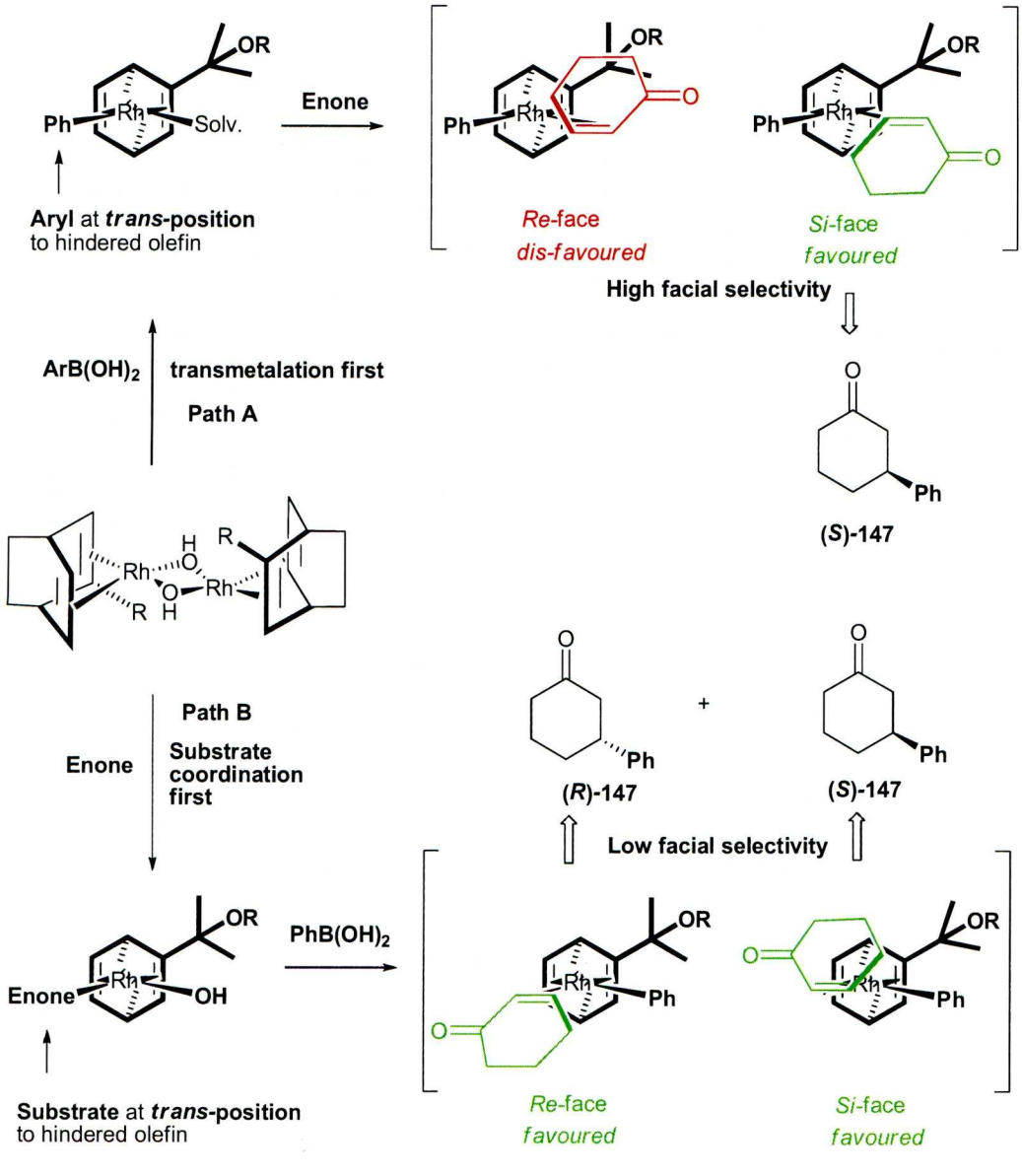
| Ligand | Yield | e.e.% |
|---|---|---|
| **42b** | 94 | 98 |

References: for compound **163**: [40, 45, 51, 52, 65, 72, 74, 80, 82, 84, 101-105]; **164**: [74, 103]; **165**: [40, 52, 72, 74, 79, 82, 105, 106]; **166**: [45, 49-51, 80, 82, 101, 104, 106]; **167**: [107]; **168** and **169**: [108]; **170**: [48, 51, 109]; **171**: [47, 51]; **172**: [65]; **173**: [110]; **174**: [78, 79, 107]; **175**: [103]; **176**: [111].

Although the diene ligands or the diene-heteroatom hybrids ligands have shown very

high enantioselectivity and activity, there are still some issues to be addressed with this new group of ligands:

1) Generally, $C_2$ or pseudo-$C_2$ (eg. **26** and **29** type) symmetric ligands were much less sensitive to the substituted groups on the olefin than the $C_1$ symmetric ligands where the enantioselectivity is concerned [102, 112]. In other words, it means that the $C_2$ or pseudo-$C_2$ symmetric ligands could guarantee a higher enantioselectivity with a phenyl or other equally bulky group on the alkene and generally there is not much difference between them. However, for the $C_1$ symmetric ligands, particularly the mono substituted diene ligands, the enantioselectivity could change greatly even with a slight change on the substituted groups [102]. As a result, a larger library of $C_1$ symmetric ligands is normally necessary in order to find the best one compared with the $C_2$ symmetric scaffolds.
2) Following the issues mentioned above, the reason why some $C_1$ symmetric ligands with only mono substituted groups, like **40** and **41**, can also achieve high enantio-selectivity remains unknown [45]. The only explanation is that the substrate is co-ordinated at the *cis*-postion of the olefin which has the bulky substituted group, while the aryl is *trans*-position, which suggests that trans-metallation step is superior to the substrates co-ordination step (so that the aryl group will prefer the *trans*-position of the bulky olefin and leave the substrate to occupy it. See Path A in ***Scheme 1.4.3***). However, the controversy is that kinetic studies reveal that the rate limiting step in this reaction is the trans-metallation step [50, 100]. It is notable that same phenomenon was observed in the additions to imine [50].




***Scheme 1.4.3*** chiral recognition model of $C_1$ symmetric mono substituted chiral diene ligand

3) The influence of the double-bond geometry of the substrates remains un-studied as yet. The substrates studied were mainly cyclic (*cis*) or *trans*-acyclic enones. The comparison between a pair of structural isomers such as *trans* and *cis* acyclic enones was not yet been reported.

4) The substrates studied were mainly focused on active Michael acceptors, for some less-active substrates like coumarin, the olefin ligands show low activity [103].

5) Although there have been quite a few examples of catalysts based on metals like Ru, Pd, and Ni and chiral phosphino or amido ligands [94], so far Rh is the only successful metal for this asymmetric transformation when chiral olefin ligands are used. Ni and a chiral alkyne ligand were tried but the enantioselectivity was quite low [113].

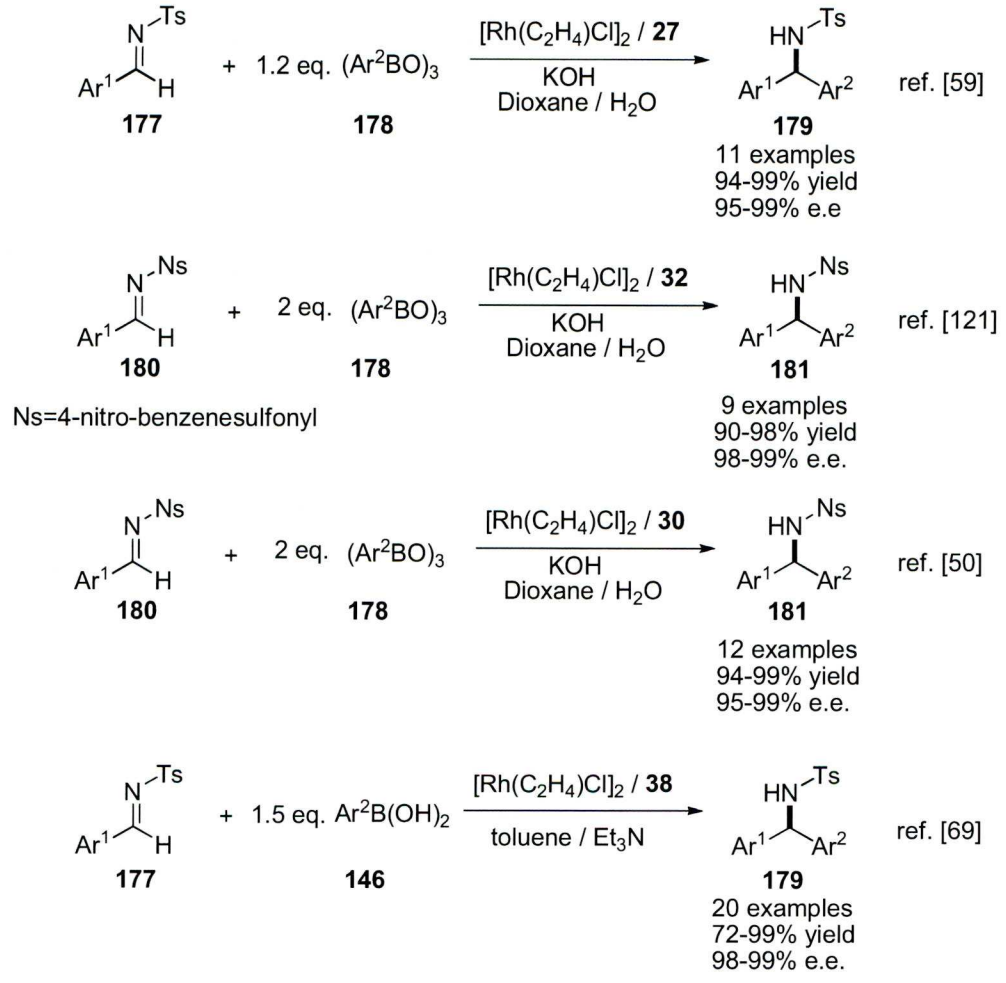
Due to the great success in application of chiral diene-Rh complexes in the ACA reactions, research toward this issue is still going on. Most recently, Hayashi group reported a highly both regioselective and enantioselective 1,6-conjugate addition of arylboronic acid to α,β,γ,δ-unsaturated carbonyl compounds using 2,5-Me-**42** iridium complex as catalyst [114]. Lin and co-workers realized the 1,4-conjugate addition of arylboronic acids to nitroalkenes using chiral diene **38** Rh complex [115].

**Addition to imines and aldehydes:**

Chiral diarylmethyl amines [116]or alcohols [117, 118] are important structural motifs that appear in many pharmaceuticals and natural products. A direct 1,2-addition to imines or aldehydes provids a straightforward way to access these compounds. There are a few examples of Rh-phosphine-catalyzed addition to imines or adehydes, however these methodologies usually suffer problems such as narrow substrates tolerance [119] or low e.e. [59, 120].

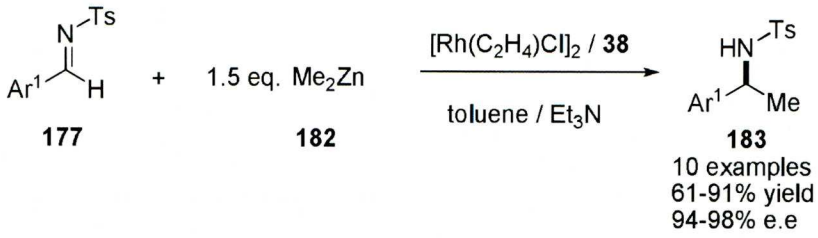
Again, diene ligands showed better performances in the arylation of imines than the phosphine ligands. Ligand **27** was successfully applied for a highly enantioselective 1,2-addition of a range of arylboroxines to *N*-tosylimines (***Scheme 1.4.4***) [59]. Due to the difficulty of removal of tosly group, an easily removable Ns (4-nitrobenzenesulfonyl) group was used instead and an improved procedure for this type of substrate was realized by using **30** as the ligands [50]. Ligand **32** was found to be an excellent scaffold for the arylation of *N*-Ns imines, and could give better enantio-selectivity with some substrates, for which diene **26** and **27** did not perform well [121].

For the aryltoslyimine addition, the ligand **38** reported by Lin and co-workers provided excellent enantioselectivity in the range of 98-99% and good to excellent yield 72-99% (20 examples) [69]. It is notable that instead of arylboroxines, which need to be synthesized from arylboronic acid prior to use, arylboronic acid was used directly in this transformation, which makes this transformation more straightforward and atom efficient.



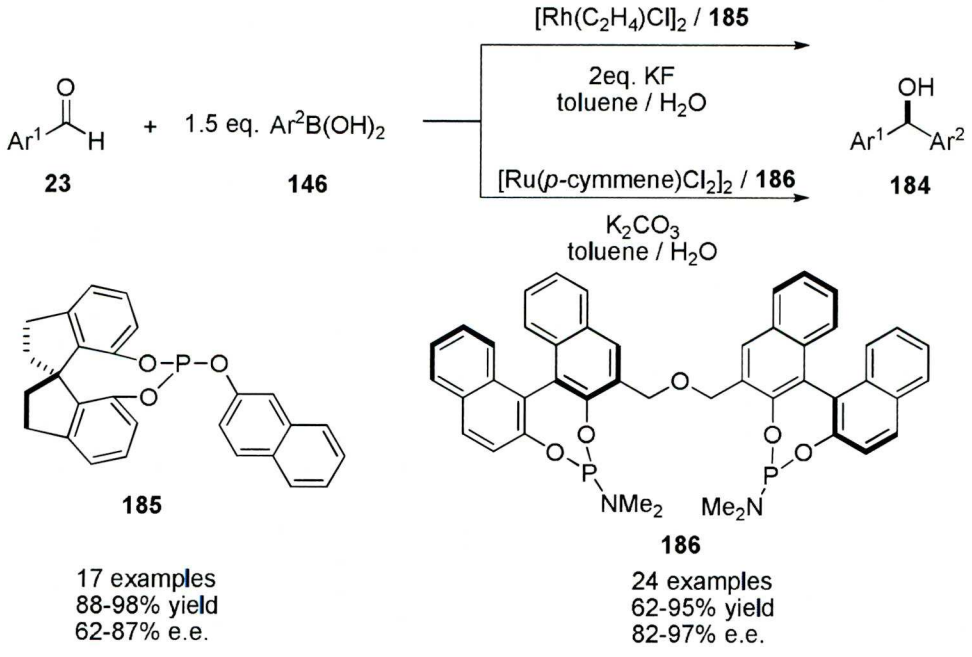

***Scheme1.4.4*** Rh-diene catalyzed asymmetric arylation of *N*-protectedimines

By using dimethylzinc as the alkyl source and chiral diene **27**-Rh as catalyst, the methylation of tosyl imine **177** was realized in good yield and high enantioselectivity. (***Scheme 1.4.5***) [120]




***Scheme1.4.5*** Rh-diene catalyzed asymmetric methylation of *N*-tosylarylimines

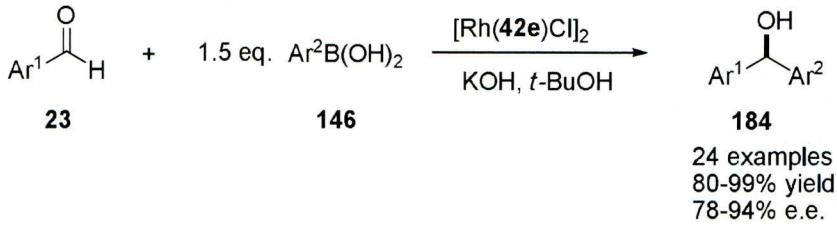
The asymmetric addition of arylboronic acids to aldehydes remains challenging [122-126]: the best results so far were obtained using Rh and a chiral spiro monophosphite compex **185** [127] (***Scheme1.4.6***) with excellent yield but only a moderate to good enantioselectivity being obtained. Excellent results were achieved by Miyaura and co-workers [128]. By using Ru and a chiral phosphoramidite ligand **186** as catalyst, both excellent yield and enantio-selectivity were achieved (average yield of *ca.*87% and e.e. of *ca.* 90%).




***Scheme1.4.6*** Rh-diene catalyzed asymmetric arylation of Arylaldehyde

The chiral diene-Rh catalyzed addition of arylboronic acids to aldehydes had not been reported until the **42e** was used in this reaction [67]. The chiral diarylmethylalcohol

**184** was obtained in high yield and e.e. ( averge yield of >90% and e.e. of 85%)

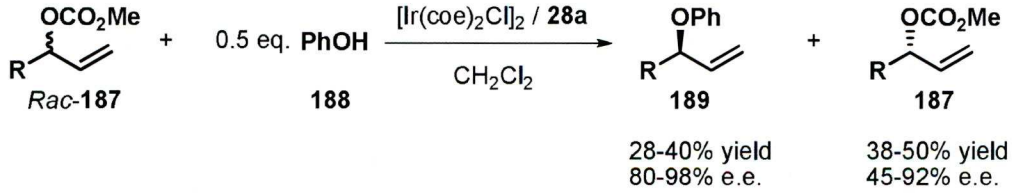



***Scheme1.4.7*** Rh-diene catalyzed asymmetric arylation of Arylaldehyde

## 1.5 Miscellaneous applications of chiral olefin ligands

**Chiral diene-Ir complex-catalyzed allylic substitutions for kinetic resolution**:

An early application of a chiral diene, which helped to demonstrate the concept that chiral dienes could be useful ligands in asymmetric catalysis, was the use of a chiral diene-Ir complex for the kinetic resolution of racemic allylic carbonates (***Scheme 1.5.1***) [41].

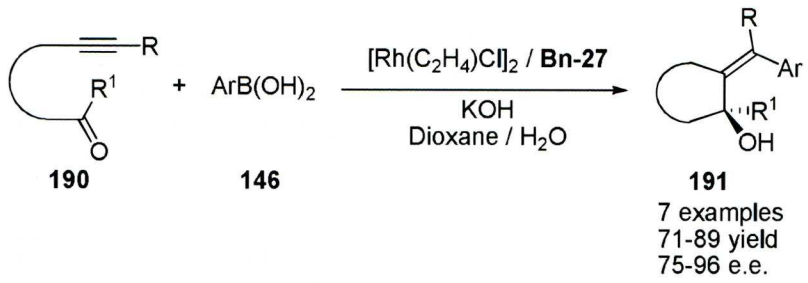



***Scheme 1.5.1*** Ir-diene catalyzed kinetic resolution of allylic carbonates

**Rh-diene –catalyzed carbocyclization through tandem reactions**

Transition metal-catalyzed tandem reactions involving multiple carbon-carbon bond formations are powerful methods for the preparation of structurally complex molecules in a convergent manner from relatively simple precursors [129, 130].

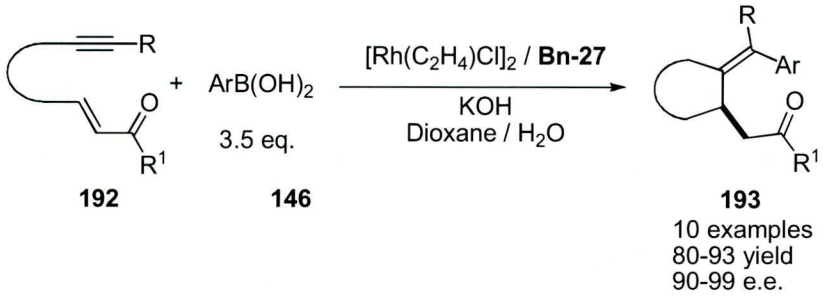
Hayashi and co-workers reported a chiral diene-Rh catalyzed addition/cyclization of arylboronic acids to alkynals, which leads to cyclic allylic alcohols with a tetrasubstituted olefin **191** (***Scheme 1.5.2***) [131];




***Scheme1.5.2*** Rh-diene catalyzed arylative cyclization of alkynals

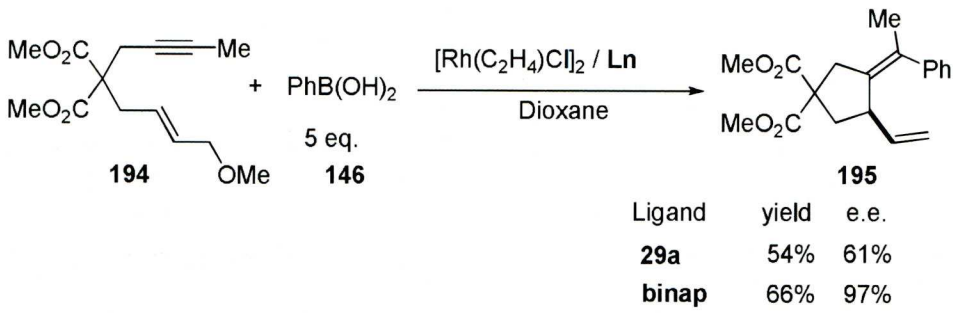
The aryl rhodium species firstly underwent *syn* addition to the triple bond to form a alkenyl rhodium intermediate which sequentially attacked the aldehyde or the kotone moiety.

A similar strategy was applied to substrate **192,** in which an α,β-unsaturated ester or ketone moiety, tethering to the alkyne group, was chosen to accept the alkenyl rhodium that formed by same mechanism (***Scheme 1.5.3***) [132]. The alkenyl rhodium intermediate undergoes an intramolecular conjugate addition to form the product **193** in high yield and excellent e.e.



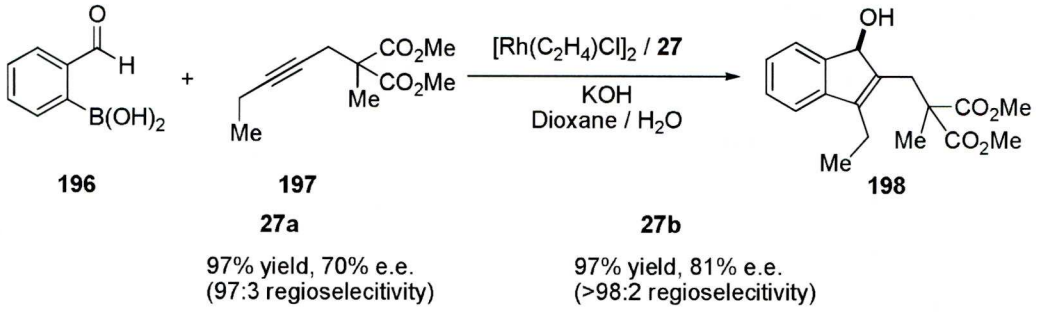

***Scheme1.5.3*** Rh-diene catalyzed arylative cyclization of alkynals

In an other case, if an appropriate allylic function group was tethered to the alkyne, the carborhodation would be followed by allylic substitution to give product **195** in moderate e.e. In this example, phosphine ligands performed better than the chiral diene ligand (***Scheme 1.5.4***) [133].



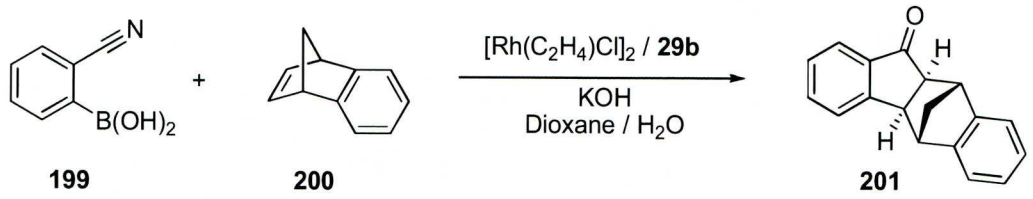

***Scheme1.5.4*** Rh-diene catalyzed arylative cyclization of alkynals

Followeing the same mechanism of addition / cyclization to alkynals, a similar cyclic allylic alcohol could be construted by the rhodium-catalyzed addition-cyclizaton of 2-formylphenylboronic acid with internal alkynes. Remarkable regio-selectivity and an excellent yield were achieved by using diene ligands. In one example, chiral diene **27** gave the product **198** in enantioselecitive manner and maintained the high regio-selectivity (***Scheme 1.5.5***) [134].




***Scheme1.5.5*** Rh-diene catalyzed synthesis of Indenols

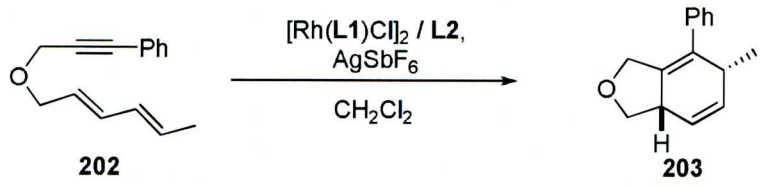
In a similar same way, 2-cyanophenylboronic acid **199** and norbornene derivatives **200** reacted to give product **201** [135]: transmetallation gives the 2-cyanophenylrhodium species which can add to the strained C=C bond and sequentially attack the cyano group. Hydrolysis *in situ* gives the final product and the re-generates of the catalyst.

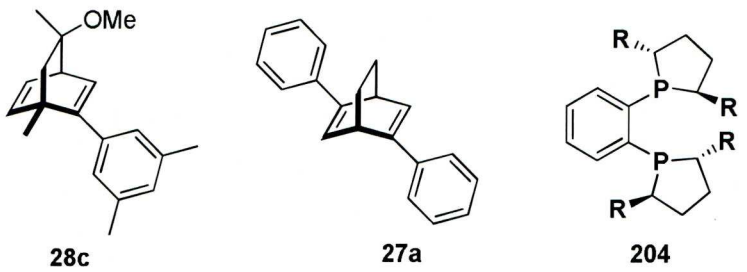



***Scheme1.5-6*** Rh-diene catalyzed synthesis of Indenols

An impressive reaction of intra-molecular [4+2] cycloaddition can be catalyzed by diene-Rh cation complexes (***Table 1.5.1***).

***Table 1.5.1*** Rh cation catalyzed [4+2] cycloaddition



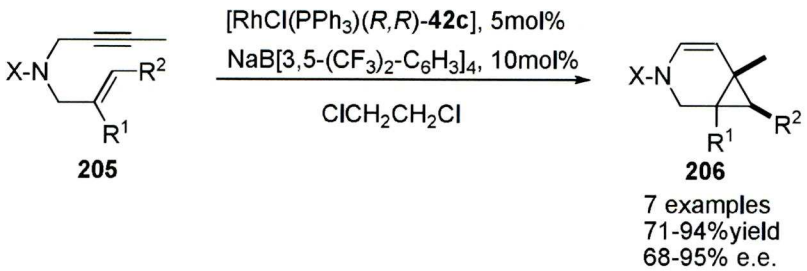




| | catalyst | | | | |
|---|---|---|---|---|---|
| entry | **L1** | **L2** | yield | e.e. | ref. |
| 1 | **28** | --- | 91 | 26 | [136] |
| 2 | **COD** | **204** | 99 | 13 | [136] |
| 3 | **28** | **204** | 99 | 95 | [136] |
| 4 | **27** | --- | 90 | 96 | [137] |
| 5 | --- | **204** | 9 | 44 | [137] |

An interesting phenomenon was observed in the initial report by Mikami and co-workers [136]. In this reaction either chiral diene **28** or chiral phosphine ligand **204**

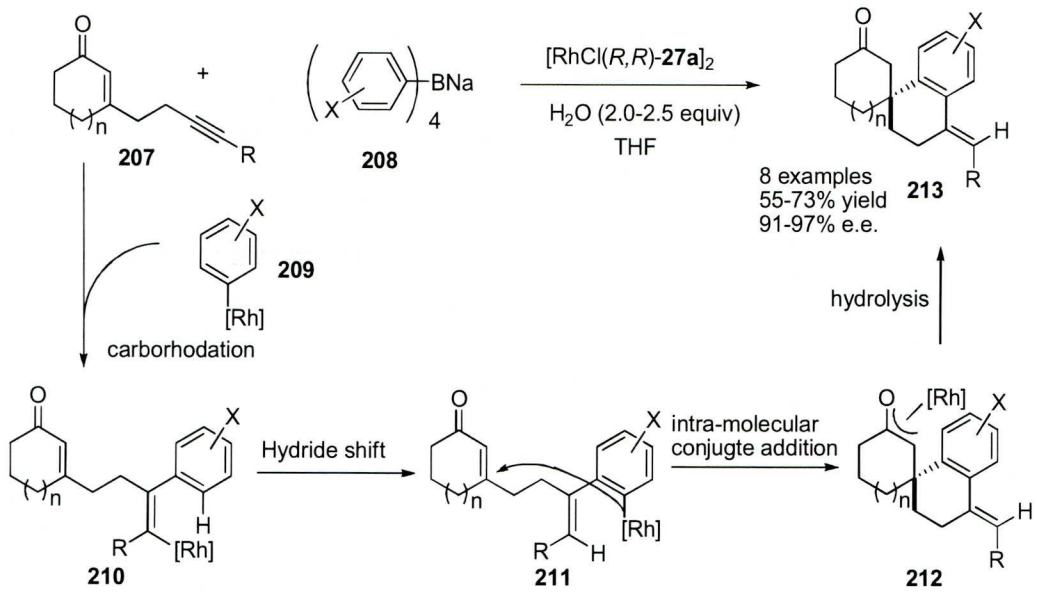
did not give high enantio-selectivity if used in isolation. High enantioselectivity was achieved only when they were used in combination (entry 1-3, ***Table 1.5.1***). Later, Hayashi's results [137] helped to clarify this observation: 1) Olefin ligands are crucial for the activity for this reaction (comparing entry 2 and 5), 2) The $C_2$-symmetric diene can gave high enantio-selectivity solely without the help of chiral phosphine and shows that the $C_2$-symmetric structure (bis substituted diene) is superior to the $C_1$-symmetric one (mono substituted diene).

Most recently, a rhodium chiral diene cation catalyzed cycloisomerization was reported by Hayashi and co-workers. In this case, a combination of triphenylphosphine ligand and electron poor chiral tfb ligand (*R,R*)-**42c** proved to be the best catalyst to realize this transformation (***Scheme 1.5.7***) [138] .




***Scheme1.5.7*** Rh-chiral diene cation catalyzed cycloisomerization.

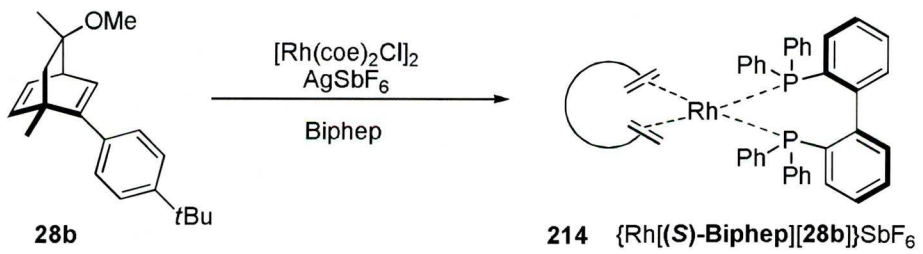
An innovative methodology to access chiral spirocarbocycles, which involves a C-H activation step in the mechanism, was demonstrated by Hayashi and co-workers recently (***Scheme1.5.8***) [139]. Transmetallation of the catalyst with sodium tetraarylborate followed by carborhodation of the triple bond in the substrate gave intermediate **210**, which underwent an intra-molecular hydride shift to give **211**: this was verified by using a deuterium labled substrate. The intermediate **211** then underwent an intra-molecular 1,4-conjugate addition followed by hydrolysis to give the desired product **213**.




***Scheme1.5.8*** Chiral diene-rhodium-catalyzed asymmetric synthesis of spirocarbocycles

**Resolution of transition metal complex**

There are other applications such the chiral diene can be resolved by stoichiometric reolution by chiral metal complex, chiral phosphine-metal complex could be resolved by chiral diene (***Scheme 1.5.9***) [140].

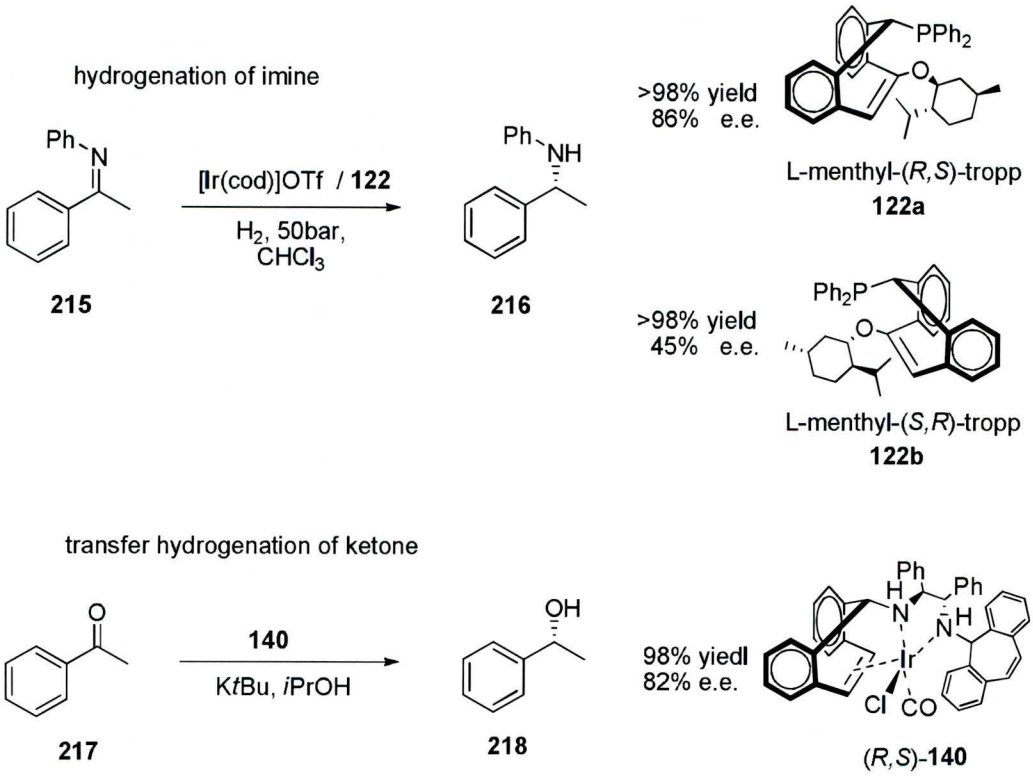



***Scheme 1.5.9*** Formation of chiral biphep-Rh complex by chiral diene ligand

**Asymmetric hydrogenation.**

In 2004, an L-menthyl containing phoshine-olefin ligand (L-menthyl-tropp) was applied to the hydrogenation of imine (***Scheme 1.5.10***) [77]. It was found that the diastereoisomers show a large difference in enantioselectivity, in which the matched

isomer **122a** gave both high yield and good e.e. but the mismatched one (**122b**) displays lower enantioselectivity. Also based on the tropp framework, the amino-olefin ligand **140** was used in the transfer-hydrogenation of acetophenone (***Scheme 1.5.10***). Although the enantioselectivity is not comparable with currently mature methodology, it provides an alternative and could be helpful to understand more about the mechanism of hydrogenation.




***Scheme 1.5.10*** Asymmetric hydrogenations of imines with phosphine-olefin ligands

**Summary and outlook**

Since the first successful application of a chiral diene ligand, there have been numerous reports of new ligands or new applications, and the research in this area is flourishing. However, compared with phosphine ligands, chiral diene ligands are much less well developed in terms of both in variety and number of applications. One

reason for this may be the difficulty of construction of the rigid scaffolds and resolution at appropriate stage during the synthesis. All of currently diene ligands not obtained from chiral auxiliary reagents or asymmetric catalysis need chiral HPLC resolution because traditional classical resolution methods show very low efficiency for these types of compounds. However, the advantages of these scaffolds (generally $C_2$ symmetric property) are obvious: they are easier to modify than the $C_1$ symmetric systems which normally obtained from chiral pool. In addition, the $C_2$ symmetry is normally a guarantee of high e.e.

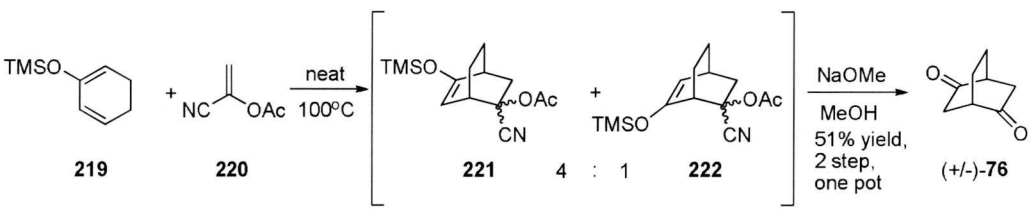
Due to the advantages of $C_2$ symmetric dienes, we envision that chemo-enzymatic approach may provide access to a wider range of structural anologues. Key to our objectives would be development of enzyme resolutions that could provide single enantiomers of ligand precursors in larger quantities than currently available by chiral HPLC.

# Chapter 2 Chemo-enzymatic synthesis of bicylco[2.2.2]octan-2,5-dione

## 2.1 Introduction

2,5-Disubstuted bicyclo[2.2.2]octan-2,5-dienes **27** are a series of useful ligands developed by Hayashi *et al.* They show novel enantioselectivity and activity in asymmetric catalytic reactions [59, 66, 99, 101, 106, 108-110, 120, 121, 132, 134, 139, 141-148]. The unsubstituted [2.2.2] bicyclic-2,5-diene is also the starting material for synthesis of CNS-modulators [149]. The chiral bicyclo[2.2.2]octan-2,5-diketones **76**, synthetic precursors to the diene compounds, are difficult to access both in terms of synthesis and resolution. This has limited the application of the diene ligands in asymmetric catalysis. For the synthesis of racemic **76**, the most frequently used route is low yielding (overall 4%) as described in Chapter 1 (page 16, ***Scheme* 1.2.8**) [150]. However, apart from the low yield and the requirement for large amounts of highly toxic lead tetra-acetate, the cheap and easily available starting materials, scalability of the reaction and straight forward purification protocols make it the best choice for gram scale preparation.

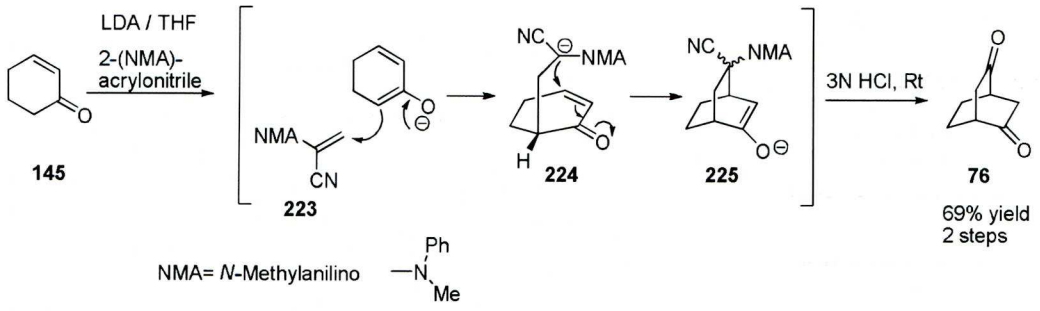
Werstiuk and co-workers reported the synthesis of racemic **76** from 2-trimethylsiloxy-1,3-cyclohexadiene **219** and cyanovinyl acetate **220** *via* Diels-Alder in a two-step one pot preparation with 51% yield [151]. However it was not commonly adapted for accessing the diektone **76**, maybe due to the high price of cyanovinyl acetate.




***Scheme 2.1.1*** Synthesis of bicylco[2.2.2]octan-2,5-dione by Diels-Alder reaction

An alternative route to compound **76** was reported by Ahlbrecht and co-workers *via*

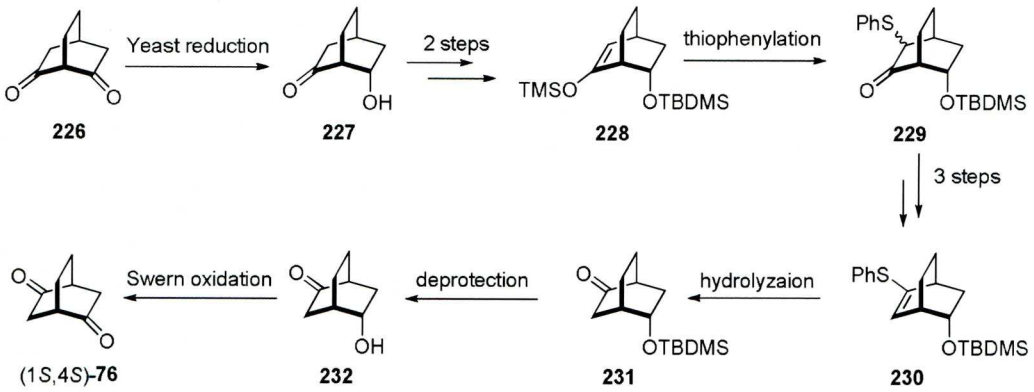
tandem-Michael addition of 1-cyanoenamine to cylcohexeones (***Scheme 2.1.2***) [152].




***Scheme 2.1.2*** Synthesis of bicylco[2.2.2]octan-2,5-dione by tandem Michael addition

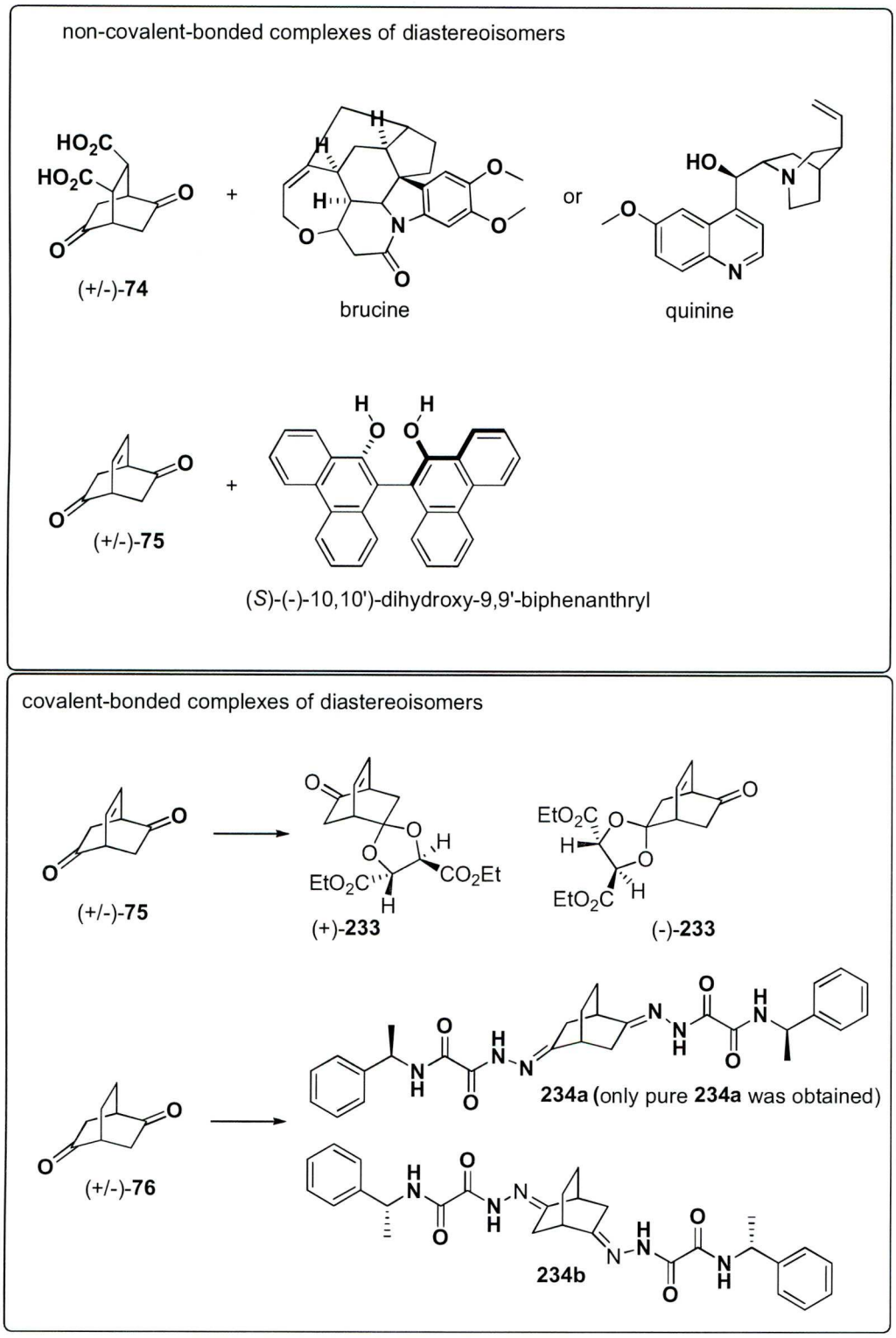
Perhaps due to the limited availability of 2-(*N*-methylanilino)-acrylonitrile, this route has also not been used for the synthesis of ligands despite having much higher synthetic efficiency than other methods.

Frejd and co-workers developed a chemo-enzymatic route for the synthesis of (1*S*,4*S*)-2,5-diketone **76** [153]. The key step is an yeast catalyzed desymmetrization of the 2,6-diketone **226** [154, 155], from which (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one (-)-**227** was obtained in high yield with 98% e.e. (-)-**227** *via* a 1,2-carbonyl transfer route [156] using a series functional group transformations to give **232**, which could be easily oxidized to give the desired (1*S*,4*S*)-**76**.




***Scheme 2.1.3*** Chemo-enzymatic synthesis of (1*S*,4*S*)-bicylco[2.2.2]octan-2,5-dione

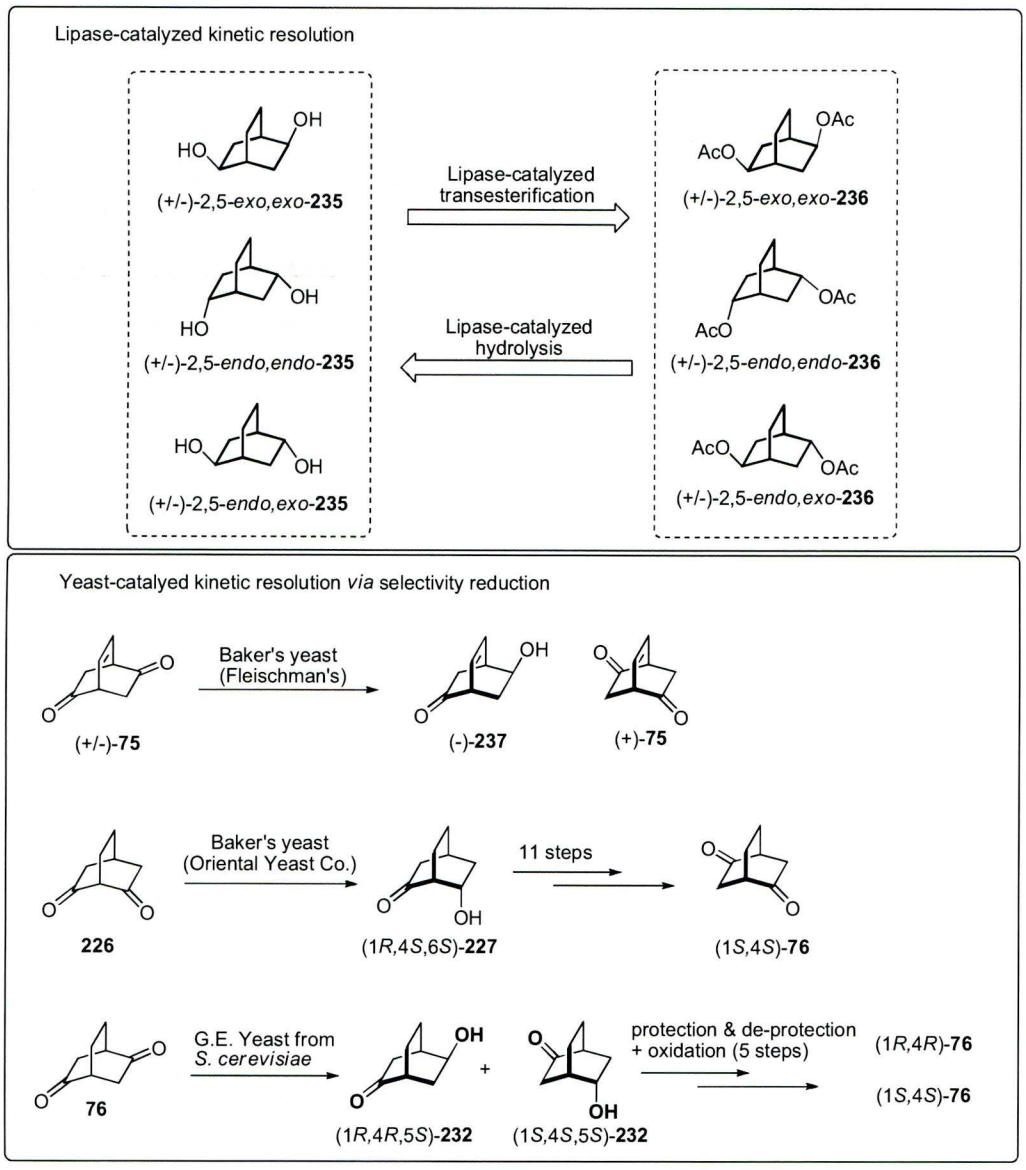
For the resolution, crystallization of diastereomeric derivatives or chiral HPLC is very inefficient. Various classical resolution methods had been applied to this diketone or its intermediates in the synthetic route, which were shown in ***Scheme 2.1.4***. The racemic **75** has been resolved as diastereomeric diethyl (*R*,*R*)-(+)-tartrate acetals [150] and as an inclusion complex with (*S*)-(-)-(10,10')-dihydroxy-9,9-biphenanthryl [157], and in the work of Hill *et al.* and Lightner *et al.* the diacid **74** was also resolved as its brucine salt or quinine salt, followed by electrolysis to give (-)-**75** [150, 158]. Furthermore, the dihydrazone of compound **76**, formed with (*R*)-5-(1-phenylethyl)semioxamazide, was resolved *via* fractional recrystallization [101]. However, all these methods were inefficient for multi-gram preparation.




***Scheme 2.1.4*** Classical resoltuion towards the bicyclo[2.2.2] scaffold.

Enzymatic methods also had been tried and are summarized in ***Scheme 2.1.5***.

Naemura investigated resolution of bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.1]octane diols by lipase-catalyzed transesterification or hydrolysis reactions. For the bicyclo[2.2.2] system, the best result was obtained from the pig liver esterase-catalyzed hydrolysis of the diacetate 2,5-*endo*, *endo*-**236**, giving its mono hydrolyzed product in 29% yield and 84% e.e. [159]. The lipase YS catalyzed transesterification of the diols was only successful for the [3.3.1] system and gave no improvement for the [2.2.2] system [160]. Racemic diketone **75** was resolved by baker's yeast reduction to give hydroxyketone (-)-**237** and unreacted (+)-ketone **75** with varying e.e.'s depending on the incubation time [158]. The yeast catalyzed desymmetrization of the 2,6-diketone **226** gave (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one (-)-**227** in high yield with 98% e.e. [154, 155]. However, a 11-step synthetic procedure was required to access one enantiomer (1*S*,4*S*)-2,5-diketone **76** (***Scheme 2.1.3***). One notable result has been reported by the same group recently; compound **76** was selectively reduced to a hydroxyketone in 98% conversion and 99% e.e. for each diasteroisomer ((1*R*,4*R*,5*S*)-**232** and (1*R*,4*R*,5*S*)-**232**) by using genetically engineered *Saccharomyces cerevisiae* [161]. However, this approach suffered from low substrate concentrations and separation problems.

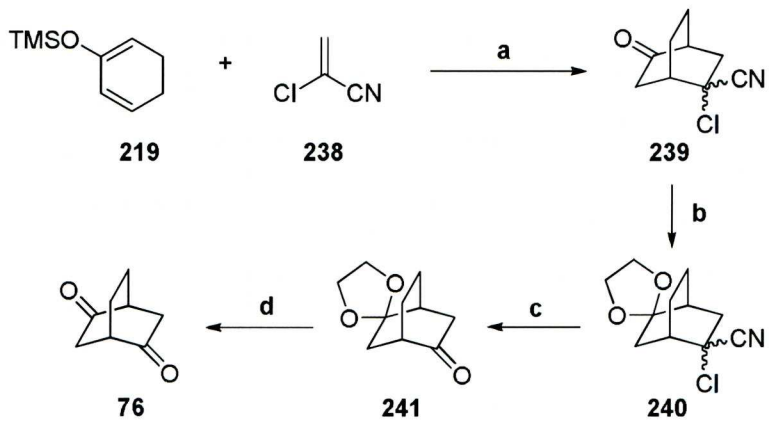



***Scheme 2.1.5*** Enzymatic resoltuion towards the bicyclo[2.2.2] scaffold.

## 2.2 Results and discussion

### 2.2.1 Synthesis of bicyclo[2.2.2]octan-2,5-dione 76

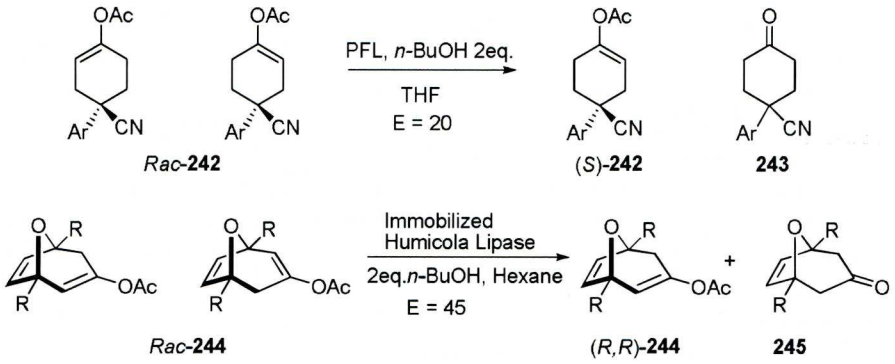
We have been exploring alternative synthetic routes and resolution methods for accessing diketone **76** and analogues in order to make the previously described asymmetric transformations accessible to the synthetic community. This has resulted in the development of a practical synthesis of homochiral diketone **76** (***Scheme 2.2.1***).




***Scheme 2.2.1*** Preparation of bicyclo[2.2.2]octan-2,5-dione **76.** Reagents and Conditions: a) Toluene, 110°C, 4hr, 70%; (b) ethylene glycol, benzene, reflux; (c) KOHaq., DMSO, Rt, 12hr, 85% two steps; (d) 10% HClaq., THF, Rt, 12hrs, quant.

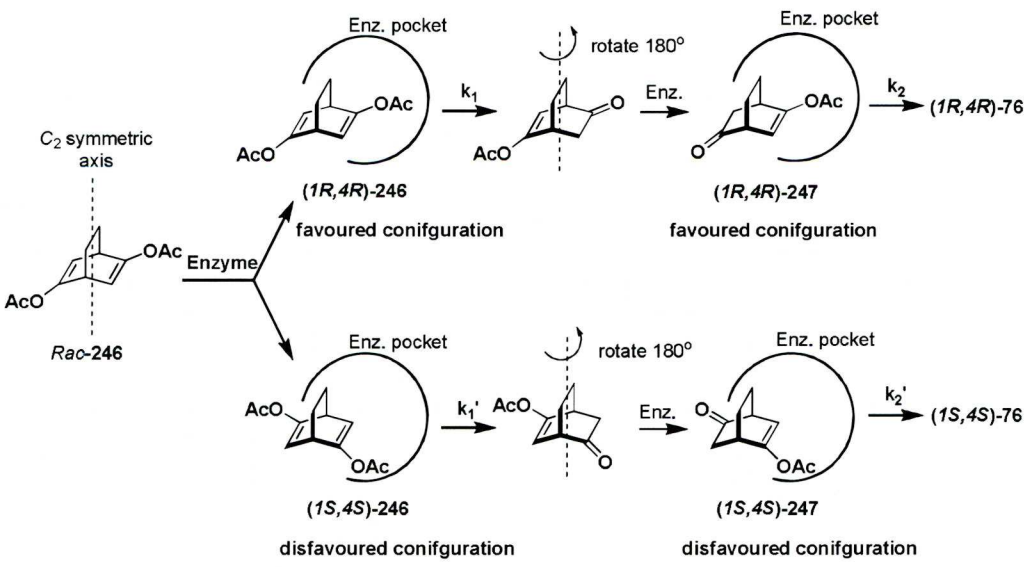
The bicyclic [2.2.2] system was constructed by [4+2] cycloaddition of 2-(trimethylsiloxy)-1,3-cylcohexadiene **219** and 2-chloroacrylonitrile **238** [162, 163]. The major product was the desired 2,5-adduct compound **239**, in which the intermediate enol silyl ether moiety was cleaved to give the ketone group during the reaction *via* some unknown mechanism. Considering the harsh conditions in converting the cyano chloro moiety into a ketone, the ketone group in compound **239** was protected with ethylene glycol to give compound **240**, which was followed by basic hydrolysis to give **241** (two steps 85% yield) [164]. Hydrolysis of the ketal group with 10% HCl / THF at room temperature afforded racemic diketone **76** in quantitative yield.

## 2.2.2 Substrates synthesis for enzyme resolution




***Scheme 2.2.2***. Lipase-catalyzed resolution of cyclic enol acetates.

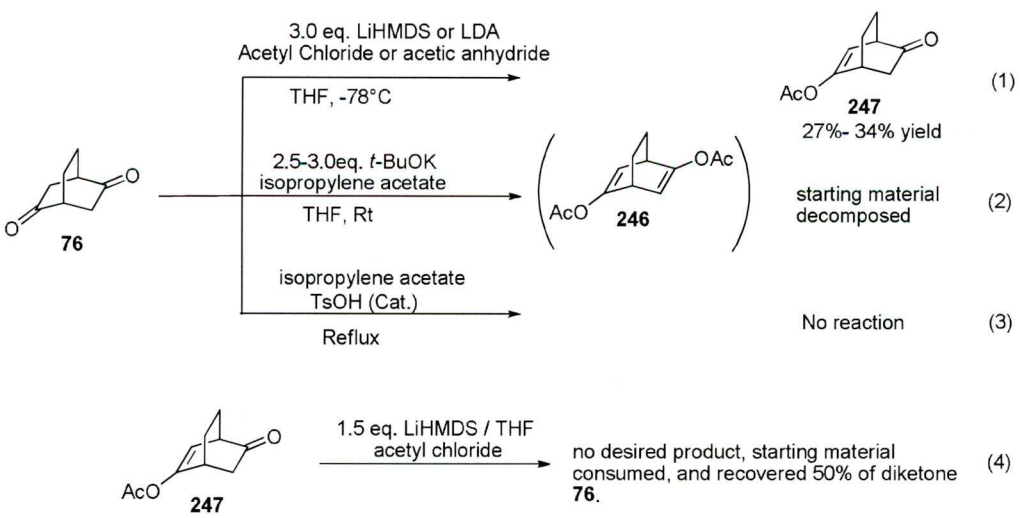
The Carnell group previously developed lipase-catalyzed resolutions of enol acetates as an effective alternative to asymmetric enolate formation for the desymmetrisation of prochiral ketones (***Scheme 2.2.2***) [165]. The enol acetate **242** was resolved with *Pseudomonas fluorescens* lipase (PFL) to provide a key building block for the synthesis of NK-2 antagonists [166-168]. Similarly oxabicyclic enol ester **244** was resolved with high selectivity using silica-absorbed *Humicola* sp. lipase [169].




***Shceme 2.2.3*** Double selective hydrolysis of $C_2$-symmetric bis-enol acetate.

Thus, we envisioned a novel resolution of diketone **76** when converted into the corresponding bis enol acetate **246** as biotransformation substrate as shown in ***Scheme 2.2.3***. In this case, if we assumed (*R,R*)-**246** to be the favored configuration, this would undergo the first hydrolysis with kinetic differentiation to give the (*R,R*)-configured monoketone compound **247**, which could rotate 180° and visit the enzyme active site again. Owing to the original $C_2$ symmetry of the *bis*-enol acetate **246**, the pseudo $C_2$ symmetric (*R,R*)-enriched mono ester **247** would be more likely to be favored, resulting in similar kinetic differentiation, although the true $C_2$ symmetry would have broken in the first step hydrolysis. If so, an amplification of the enantio-selectivity may result.

Unfortunately, our effort to synthesize the *bis*-enol acetate **246** failed (***Scheme 2.2.4***). Treatment of **76** with 3 eq. of LiHMDS or LDA and acetyl donors at -78°C gave **247** in low yield (equation 1). The procedure that has originally been used for the synthesis of enol acetate **244** was applied but yielded no product although all starting material was consumed (equation 2). Acid catalyzed transesterification also failed (equation 3).



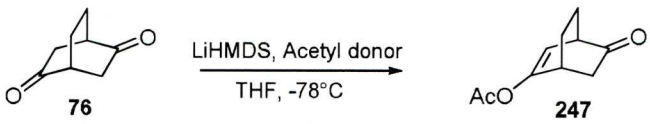

***Scheme 2.2.4*** Efforts towards the synthesis of bis-enol acetate **246**

Sequential esterification by using the product **247** obtained in equation (1) as starting

material also failed (see equation (4)).

After further screening of the conditions described in equation (1), it was found that decreasing the amount of base increased the yield of mono-enol-acetate **247**. The highest yield was obtained when 1.1 equivalent of base and 1.1 equivalent of acetic anhydride were used (***Table 2.2.1***).

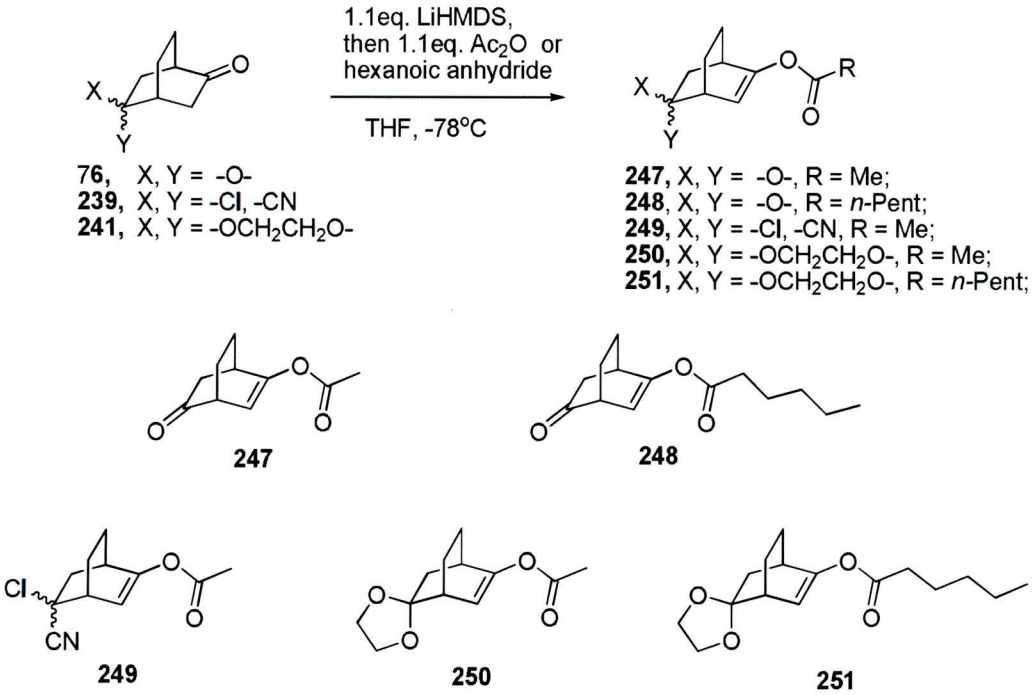
***Table 2.2.1*** Conditions screening for synthesis of enolacetate




**76** **247**

| Entry | Base | Quantity | Time | Acetone donor | yield | Temperature |
|---|---|---|---|---|---|---|
| 1 | LHMDS | 3eq. | 12hr | Acetylchloride | 40 | -78 |
| 2 | LHMDS | 3eq. | 48hr | Acetylchloride | 43 | -78 |
| 3 | LDA | 3eq. | 12hr | Acetylchloride | 8 | -78 |
| 4 | LHMDS | 3eq. | 48hr | Acetylchloride | 48 | -78-rt |
| 5 | LDA | 3eq. | 48hr | Acetic anhydride | 13 | -78-rt |
| 6 | LHMDS | 3eq. | 48hr | Acetic anhydride | 48 | -78-rt |
| 7 | LHMDS | 1.5eq. | 12hr | Acetylchloride | 90 | -78-rt |
| 8 | LHMDS | 1.5eq. | 12hr | Acetic anhydride | 88 | -78-rt |
| **9** | LHMDS | **1.1eq.** | 12hr | Acetic anhydride | **95** | -78-rt |

Consequently, we decided to use the mono enol acetate **247** for the enzyme resolution. In addition, a number of other enol esters were synthesized for the enzyme resolution (***Scheme 2.2.5***).




***Scheme 2.2.5*** Enol acetates prepared for lipase resolution

Firstly, substrate **247** was tested using previously employed biotransformation conditions. However, there was no reaction with PFL in THF, while silica absorbed *Humicola* sp. lipase in hexane gave low selectivity. A systematic screening was carried out with a series of lipases under varied solvent conditions (***Table 2.2.2-2.2.4***).

***Tabel 2.2.2*** Lipase screen in hexane for **247**

| Entry | Enzyme | Conversion | ee% of Enolate (enolate left%) | | E |
|---|---|---|---|---|---|
| 1 | *Candida rugosa* (Chirazyme L-3, Europa Lipase AY) | 31.2 | -0.9 | (68.2) | 1 |
| 2 | *Pseudomonas fluorescens*(PFL, Amano AK30) | 8.0 | 1.4 | (92.0) | 1.4 |
| 3 | *Candida antarctica* (Lipase B, Novozyme 435) | 77.5 | 86.5 | (22.5) | 1.4 |
| 4 | *Pseudomonas cepacia* (PCL, Lipase PS Amano) | 3.7 | -5.0 | (96.3) | -- |
| 5 | *Mucor javanicus* (Lipase Amano 10) | 3.3 | 0 | (96.7) | -- |
| 6 | *Penicillium camembertii* (Lipase G Amano 50) | 24.7 | 14.1 | (75.3) | 3 |
| 7 | *Rhizopius oryzae* (Lipase F AP-15) | 4.0 | 0 | (96.0) | -- |
| 8 | *Mucor meihei* (Lipase M Amano,Europa lipase 15(RS)) | 0 | -- | (100) | -- |
| 9 | *Candida antarctica* (chirazyme L-2 ) | 65.9 | 60.1 | (34.1) | 3.3 |
| 10 | *Alcaligenes sp.* (Europa Lipase 20) | 11.9 | 5.0 | (88.1) | 2.3 |

***Table 2.2.3*** Lipase screen in toluene for **247**

| Entry | Enzyme | Conversion | ee% of Enolate (enolate left%) | | E |
|---|---|---|---|---|---|
| 1 | *Candida rugosa* (Chirazyme L-3, Europa Lipase AY) | 0 | – | (100) | – |
| 2 | *Pseudomonas fluorescens*(PFL, Amano AK30) | 0 | – | (100) | – |
| 3 | ***Candida antarctica* (Lipase B, Novozyme 435)** | **11.8** | **12.4** | **(88.2)** | **17** |
| 4 | *Pseudomonas cepacia* (PCL, Lipase PS Amano) | 0 | – | (100) | – |
| 5 | *Mucor javanicus* (Lipase Amano 10) | 0 | – | (100) | – |
| 6 | *Penicillium camembertii* (Lipase G Amano 50) | 0 | – | (100) | – |
| 7 | *Rhizopius oryzae* (Lipase F AP-15) | 0 | – | (100) | – |
| 8 | *Mucor meihei* (Lipase M Amano,Europa lipase 15(RS)) | 0 | – | (100) | – |
| 9 | ***Candida antarctica* (chirazyme L-2 )** | **11.3** | **14.8** | **(88.7)** | **16** |
| 10 | *Alcaligenes sp.* (Europa Lipase 20) | 3.5 | 5.0 | (98.5) | – |

***Table 2.2.4*** Lipase screen in buffer for **247**

| Entry | Enzyme | Conversion | ee% of Enolate (enolate left%) | | E |
|---|---|---|---|---|---|
| 1 | *Candida rugosa* (Chirazyme L-3, Europa Lipase AY) | 100 | -- | (0) | -- |
| 2 | *Pseudomonas fluorescens*(PFL, Amano AK30) | 39.2 | 21.0 | (60.8) | 2.4 |
| 3 | *Candida antarctica* (Lipase B, Novozyme 435) | 55.3 | 69.4 | (44.7) | 7 |
| 4 | *Pseudomonas cepacia* (PCL, Lipase PS Amano) | 8.8 | 0 | (91.2) | -- |
| 5 | *Mucor javanicus* (Lipase Amano 10) | 11.4 | -5.5 | (88.6) | 2.6 |
| 6 | *Penicillium camembertii* (Lipase G Amano 50) | 29.6 | 14.4 | (70.4) | 2.4 |
| 7 | *Rhizopius oryzae* (Lipase F AP-15) | 100 | -- | (0) | -- |
| 8 | *Mucor meihei* (Lipase M Amano,Europa lipase 15(RS)) | 31.5 | -2.52 | (68.5) | 1.1 |
| 9 | *Candida antarctica* (chirazyme L-2 ) | 34.1 | 20.8 | (65.9) | 3.0 |
| 10 | *Alcaligenes sp.* (Europa Lipase 20) | 24.7 | 13.0 | (75.3) | 2.6 |

All reactions were carried as follows: for transesterification reactions in toluene and hexane, 10mg of substate, 2eq. of nBuOH to the substrate, and 5ml of solvent. For hydrolytic reaciton in buffer, except without addition of nBuOH, the rest are same. All reactions are stirred at room temperature for 12 hr.

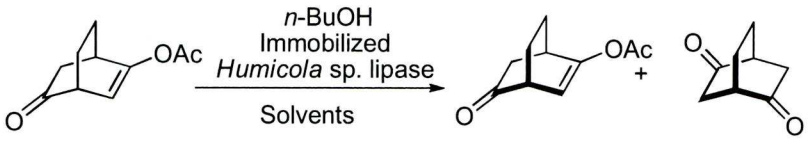
Only CAL-B (*Candida antarctica*) showed a moderate enantioselectivity for this substrate in toluene ($E$ = 16 and 17, entries 3 and 9, ***Table 2.2.3***), with a very low reaction rate. The results of screening with substrates **248** – **251** showed either low reactivity or low enantioselecitivty.

### 2.2.3 Kinetic resolution of (+/-)247 using immobilized *Humicola* sp. lipase

Given our previous success with immobilized *Humicola* sp. lipase for the bicyclic compound **244** (page 61, ***Scheme 2.2.2***, Chapter 2) [169], further investigations were focused on this enzyme. Various immobilization methods and solvents were tried (***Table 2.2.5***).

Although solvent screening showed that the *Humicola* sp. lipase had tolerated a narrow range of solvents for this compound (it only works in nonpolar alkanes), exciting results were obtained when it was immobilized on PhosES-03 and Accurel with pentane as the solvent (entries 18 and 19), where the E values are as high as 116 and 68 respectively. Comparing the supporting materials between entry 18 and 19, Accurel is polypropylene powder with c.a. 250 μm size, with a large hydrophobic alkane surface; and the PhosES-03 is silica highly modified with long chain alkanes on the surface. Entries 10, 15 and 16 (the PhosES-01, normal silica gel from Posphonic company), with unfunctionalized surface silanol groups, have much lower E values than entries 18 and 19. Moreover, the supporting material PhosES-02 (entry17) is silica which was moderately modified (less than PhosES-03) with long chain alkane. In this case the E value was 40 which is higher than entries 10, 15 and 16 but lower than 18 and 19. These results indicate that the more hydrophobic the support system, the better the enantioselectivity the enzyme.

***Table 2.2.5*** Screening with *Humicola* sp. lipase




(+/-)-**247** (*R,R*)-**247** (*S,S*)-**76**

| entry[a] | Solvents | Immobilization | conversion %[i] | e.e. %[j] | reaction time | *E* value |
|---|---|---|---|---|---|---|
| 1 | Toluene | Silica[g] | No reaction | -- | 4d | -- |
| 2 | TBME | Silica[g] | 41 | 43 | 4d | 6 |
| 3 | $Et_2O$ | Silica[g] | 27 | 13 | 4d | 2 |
| 4 | DME | Silica[g] | No reaction | -- | 4d | -- |
| 5 | Acetone | Silica[g] | No reaction | -- | 4d | -- |
| 5 | Hexane | Silica[g] | 60 | 73 | 2d | 6 |
| 7 | Cyclohexane | Silica[g] | 31 | 28 | 1d | 5 |
| 8 | Heptane | Silica[g] | 29 | 26.6 | 1d | 6 |
| 9 | Petroether | Silica[g] | 27 | 25.7 | 1d | 5 |
| 10 | Pentane | Silica[g] | 31 | 37 | 1d | 15 |
| 11[b] | Pentane | lyophilized[g] | 42 | 45 | 6d | 6 |
| 12[b] | Pentane | lyophilized[h] | 14 | 15 | 4d | 27 |
| 13 | Buffer | Enz. solun | 24 | 13 | 2d | <1 |
| 14[c] | Pentane | PCMC[g] | 29 | 31 | 0.5d | 10 |
| 15[d] | Pentane | Sol-gel[g] | 29 | 37 | 3d | 29 |
| 16[e] | Pentane | PhosES-01[h] | 25 | 30 | 1d | 25 |
| 17[e] | Pentane | PhosES-02[h] | 34 | 48 | 10hr | 45 |
| **18[e]** | **Pentane** | **PhosES-03[h]** | 21 | 26 | 30hr | **116** |
| **19[f]** | **Pentane** | **Accurel[h]** | 30 | 41 | 3hr | **68** |
| 20[f] | Pentane | Accurel[g] | 52 | 90 | 5hr | 33 |
| 21 | Pentane | Eupergit[h] | 30 | 22 | 3d | 4 |
| 22 | Pentane | Eupergit[g] | 34 | 40 | 2d | 12 |

(a) All reactions were carried out as follows: 10mg of substrate, 2eq. of *n*-BuOH w.r.t. the substrate, and 5ml of solvent. For each immobilized enzyme assay, 50 uL of enzyme solution was used. The supporting material varies. For silica, 200mg was used in each assay, for the PhosES series silica 100mg was used for each assay, (b) 2mg of free dried enzyme was used, (c) PCMC method was used according to ref. [170], (d) The sol-gel and Eupergit adsorption was done according to the ref. [171], (e) PhosES01-03 were silica materials given by PhosphonicS Ltd., (f) The Accurel adsorption was done according to the ref. [172], (g) dry catalyst, (h) catalyst containing water, (i) conversion determined by GC, (j) E.e. was determined with chiral HPLC on Chiracel AD column.

It can be concluded from ***Table 2.2.5*** that generally the immobilized enzyme shows better selectivity than the free enzyme (comparing entry 10 with 11), which is consistent with the literature result where *Humicola* sp. lipase shows increased selectivity after immobilization on silica [169]. This could be attributed to a conformational change within the active site.

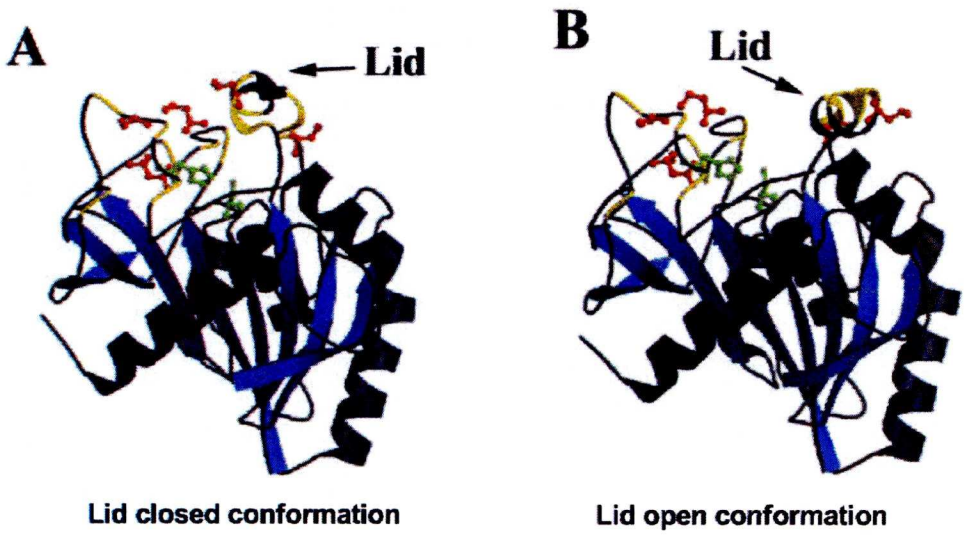



***Figure 2.2.1*** Three-dimensional structures of the closed form (A) and of the open form (B) of *Humicola* sp. lipase (ref.[173]). Carboxylic side-chains Asp-96, Asp-201, Asp-254, Glu-87, Glu-210 (in red) lie at the periphery of the external hydrophobic region (in yellow). The catalytic triad (in green) becomes accessible after opening the lid. The rotation of the lid exposed hydrophobic residues of the amphiphilic helix at the external surface of the enzyme.

The results of Noinville *et al.* indicate that the hydrophobic lid which covers the active site of *Humicola* sp. lipase is in the open conformation at the water-hydrophobic interface (***Fig 2.2.1***) [173]. Thus, immobilsation on a hydrophobic surface which has associated water seems to be essential in our reactions. It may facilitate such a conformational change resulting in increased reactivity and selectivity. If we compare entry 11 with 12 and entry 19 with 20, it can be seen that with free enzyme (entry 11 and 12) or immobilized enzyme (entry 19 and 20), a small amount

of water is advantageous: entry 12 is better than 11, and 19 is much better than 20.

Due to the successful performance achieved by *Humicola* lipase, which is isolated from the *Rhizomucor* family of fungi, other lipases from the *Rhizomucor* family were screened under the same conditions. However, the results show that none of them outperform or even come close to *Humicola* lipase. All of them show very low activity and low enantioselectivity (***Table 2.2.6***).

***Table2.2.6*** Screen with lipases from *Rhizomucor* family for resolution of (+/-)-**247**

| entry | Enzyme | conversion | e.e. | *E* value |
|---|---|---|---|---|
| 1 | *Aspergillus niger* (ANL) | <3 | N.D. | --- |
| 2 | *Rhizomucor* (RML) | no reaction | N.D | --- |
| 3 | *Rhizopus* (ROL) | 21 | 12 | 3 |
| 4 | *Penicillum camembertii* (RcamL) | no reaction | N.D. | --- |
| 5 | *Candida antarctica* (CAL-A) | 10 | -3.7 | 1.7 |

All reactions were carried out same as that in ***Table 2.2.5*** and quenched after 24hrs.

The effect of *n*-butanol was also studied and was found to have a pronounced effect on the activity and enantioselectivity (***Table 2.2.7***). On increasing the *n*-butanol from 2 eq. to 5eq., the the reactivity dropped dramatically. The reactivity of the lipase remained at a low level and steadily decreased when the ratio of *n*-BuOH over substrate was increased from 5 to 100.

***Table2.2.7*** Screen with amount of *n*-Butanol for resolution of (+/-)-**247**

| entry | *n*-BuOH/subs. | Reaction time | e.e | Conversion | *E*-value |
|---|---|---|---|---|---|
| 1 | 5 | 12hr | 18 | 16 | 41 |
| 2 | 10 | 12hr | 12 | 14 | 7.4 |
| 3 | 20 | 12hr | 8 | 10 | 6.6 |
| 4 | 40 | 12hr | 5 | 8 | -- |
| 5 | 100 | 12hr | 0 | 3 | -- |

All reactions were carried out same as entry 19 in ***Table 2.2.5*** (immobilized *Humicola* sp. lipase on accurel) except that the amount of *n*-BuOH w.r.t. substrate was varied.

Other solid supports with regular three-dimension porous materials such as MCM-48 and SBA-15 were used to immobilize the *Humicola* sp. lipase and it was found that the regular porous structure did not bring extra benefit for the selectivity, the E value obtained was the same as for their amorphous silica analogue (***Table 2.2.8***).

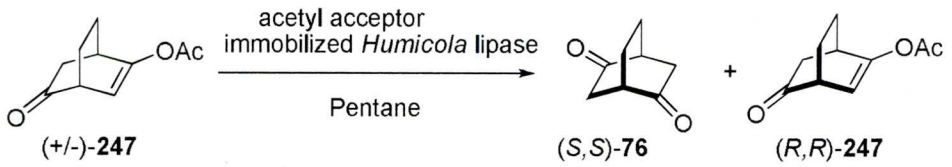
***Table 2.2.8*** Mesoporous materials as supporting materials for *Humicola* lipase biotransformation of (+/-)-**247**

| entry | supporting material | conversion | e.e. | reaction time | E value |
|---|---|---|---|---|---|
| 1 | MCM-48 | 13 | 13 | 12hrs | 3 |
| 2 | SBA-15 | 17 | 16.5 | 7d | 5 |
| 3 | SBA-16 | 9 | 7.7 | 5d | 11 |
| 4 | MCF-3 | 14 | 14 | 5d | 12 |
| 5 | MCF-6 | 12 | 12 | 30hr | 10 |
| 6 | MCF-10 | 8.8 | 7 | 3d | 10 |

All immobilizaitons and reactions were carried out as that in ***Table 2.2.5***

It had been found that the immobilized wet *Humicola* lipase outperformed the dry catalyst. Considering that water can also act as a nucleophile to accept the acyl group, experiments without *n*-BuOH were run and it was found that on a small scale the rate was not affected. (entries 1 and 2, ***Table 2.2.9***). However, the activity dropped remarkably when the reaction was scaled up to 1 gram scale. It is believed that the acetic acid produced along with the hydrolysis prohibits the reaction and decreases the *E* value [174].

***Table 2.2.9*** Water containing immobilized *Humicola* lipase reslotuion




(+/-)-**247** (*S,S*)-**76** (*R,R*)-**247**

| Entry | Cat | Acetyl aceptor | reaction time | conversion% | e.e.% |
|---|---|---|---|---|---|
| 1[a] | PhosES03 | water | 1.5hr | 65 | 100 |
| 2[a] | Accurel | water | 1.5hr | 58 | 100 |
| 3[b] | PhosES03 | water/*n*-Butanol | 1.5hr | 60 | 100 |

a) Reactions were carried out same as entries 18 and19 in ***Table 2.2.5*** except without addition of *n*-BuOH, b) Conditions were same as entry 18 in ***Table 2.2.5***.

Bases were used to neutralize the acetic acid. By using same conditions as entry 2 in ***Table 2.2.9***, organic bases were introduced to be the acid scavengers (***Table 2.2.10***). It was found that the activity has increased significantly, in presence of DABCO, conversion was almost 60% in 30mins (entry 3, ***Table 2.2.9***). However the E value dropped considerably, particularly when using triethylamine (entry 1).

***Table 2.2.10*** Base screen when water was used as acetyl aceptor

| Entry | Cat | Acetyl aceptor | Base | Time | Conversion | ee | E-value |
|---|---|---|---|---|---|---|---|
| 1 | Accurel | water | $Et_3N$ | 0.5hr | 53.5 | 54.2 | 4.5 |
| 2 | Accurel | water | DIPEA | 0.5hr | 53.3 | 87 | 20 |
| 3 | Accurel | Water | DABCO | 0.5hr | 59.7 | 98.4 | 25 |

Reactions were carried out same as entries 1 and 2 in ***Table 2.2.9*** except extra base was added.

One reasonable explanation for these results is that although these organic bases may accelerate the reaction by trapping the acetic acid they may also affect the enzyme's conformation (may be by changing the pH of the reaction solution) leading to a decrease of enantioselectivity.

According to the results obtained above, the conditions for entry 19 in ***Table 2.2.5*** were chosen for scale up. However, it was found that, after the reaction was scaled up to 1gram, the reaction rate slowed significantly, requiring 5 days to get the point where the enol acetate reached >99% e.e. with 39% isolated yield. The decrease in activity maybe attributed to two factors: firstly, loss of the water by catalyst. When the reaction was scaled up in a larger vessel, it was found that when vigorously stirring for over 12 hours, the water from the solid enzyme catalyst splashed onto the wall of the reaction flask and was lost from the enzyme; secondly, the acetic acid possibily formed during the hydrolysis, which may be inhibit the reaction.

To overcome these two problems, we devised a special reactor to carry out this resolution (***Fig 2.2.2***).

***Fig 2.2.2*** Reactor for resolution by *Humicolai* sp. lipase on wet Accurel

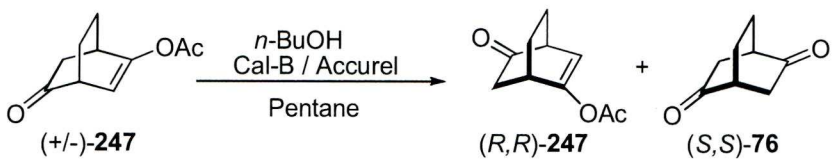
A standard laboratory vacuum desiccator was used as the reaction vessel. The immobilized enzyme was placed on the metal mesh that had been covered with cotton fabric. Sodium bicarbonate was also placed alongside the immobilized enzyme in a separate pile, in order to neutralize any acetic acid formed. This was a precaution since the reaction is a butanolysis (as evidenced from the butyl acetate formed). The reaction was stirred vigorously by a magnetic stirrer bar sitting in the bottom of the dessicator. In this way the solid enzyme and bicarbonate were not disturbed and this increased the reaction efficiency greatly compared with simply mixing the solids and allowing them to stir with the stirrer bar.

By using this apparatus, a 9.5gram scale resolution was carried out and we were pleased to find that it did work: enantiomerically pure (>99% e.e.) (*R,R*)-enol acetate **247** (3.5 g, 39% yield) and (*S,S*)-diketone-**76** (4.1 g, 59.5% yield, 64% e.e.) were obtained after the reaction running for 36hrs followed by separation.

### 2.2.4 Kinetic resolution of (+/-)-247 using immobilized Cal-B lipase

A similar immobilization strategy was applied to Cal-B lipase (***Table 2.2.11***). Preliminary solvent screening for the lyophilized Cal-B suggested that the best organic solvent was toluene, however there was no obvious improvement in both activity and enantioselectivity after immobilization on silica (entries 3 and 4).

***Table 2.2.11*** Screening with CAL-B lipase




(+/-)-**247** (*R,R*)-**247** (*S,S*)-**76**

| entry[a] | Solvents | Immobilization | conversion | e.e. | reaction time | E value |
|---|---|---|---|---|---|---|
| 1 | Buffer | Lyophilize[b] | 55 | 69 | 12hrs | 3 |
| 2 | Hexane | Lyophilized[b] | 65 | 60 | 7d | 5 |
| 3 | Toluene | Lyophilized[b] | 54 | 78 | 5d | 11 |
| 4 | Toluene | Silca[b] | 57 | 85 | 5d | 12 |
| 5 | Pentane | PCMC[b] | 58 | 85 | 30hr | 10 |
| 6 | Pentane | Sol-gel[b] | 12 | 11 | 3d | 10 |
| 7 | Pentane | PhosES01[c] | 21 | 21 | 2d | 11 |
| 8 | Pentane | PhosES02[c] | 17 | 17 | 2d | 12 |
| 9 | Pentane | PhosES03[c] | 18 | 20 | 2d | 17 |
| 10 | Pentane | PhosES03[b] | 34 | 43 | 1d | 15 |
| 11 | Pentane | Accurel[c] | -- | -- | 3d | -- |
| **12** | **Pentane** | **Accurel[b]** | **29** | **40** | **3d** | **120** |
| 13 | Pentane | Eupergit[c] | 29 | 25 | 5d | 5 |
| 14 | Pentane | Eupergit[b] | -- | -- | 5d | -- |

(a) The reaction protocols are as same as that for *Humicola* lipase when same supporting material used, (b) dry catalyst, (c) catalyst containing water.

According to Rotticci *et al.* [175], Cal-B exhibited a great increase in both activity and enantioselectivity after immobilization on Accurel EP-100 in the kinetic resolution of seudenol. We were pleased to find that the enantioselectivity was increased greatly when the CaL-B lipase was immobilized on Accurel for resolution

of enol acetate **247**. Notably, CAL-B works much better in anhydrous conditions (entry 12) than in wet conditions (entry 11), which is contrary to the findings for *Humicola* sp. lipase in this reaction.

Cal-B lipase had a very low reactivity in anhydrous conditions, except when the PCMC (protein coated micro-crystal) protocol was used (entry 5) where the reactivity increased significantly but the enantioselectivity remained at a similar level.

## 2.3 Conclusion

We have developed a synthetic route making chiral bicyclo[2.2.2]octan-2,5-dione **76** readily accessible. This method includes a practical 4-step synthetic route for the racemic diketone **76** (more than 60% overall yield) and a novel enzymatic resolution, in which the racemic diketone was converted into its corresponding mono enol acetate **247**.

The construction of the bicyclic [2.2.2] structure was realized *via* a classical Diels-Alder reaction by reacting 2-(trimethylsiloxy)-1,3-cylcohexadiene **219** with 2-chloroacrylonitrile **238**. It was crucial that the ketone group of the adduct **239** was protected by ketalization prior to basic hydrolysis of the chloro-cyano centre. Compound **239** underwent ketalization, basic hydrolysis and then deketalization to yield racemic bicyclo[2.2.2]octan-2,5-dione **76** in good yield. This synthetic route is reliable and practicable.

A screen for the enzymatic resolution for the mono enol acetate of **76** (compound **247**) was carried out. Two enzymes selected, *Humicola* sp. lipase and Cal-B lipase, showed a dramatic increase in enantioselectivity when immobilized on supporting materials with a large hydrophobic surface. For an instance, *Humicola* sp. lipase immobilized on Accurel has an $E$ value of 116 compared with the lyophilized powder ($E$ = 27). Cal-B immobilized on Accurel has an $E$ = 120 compared with 15 for the lyophilized

form. This was attributed to conformational changes of the enzymes resulting from contact with the hydrophobic solid surface.

We were pleased to find that these two enzymes give enantiocomplementary selectivity. As a result, homochiral (*R,R*)-**247** could be obtained in 39% yield by immobilized *Humicola* sp. lipase-catalyzed kinetic resolution, while enantiomerically pure (*S,S*)-**247** was obtained in 30% yield using immobilized Cal-B lipase. It is notable that the resolution can be carried out on a multi-gram scale (10g) without any reduction of enantioselectivity or activity.

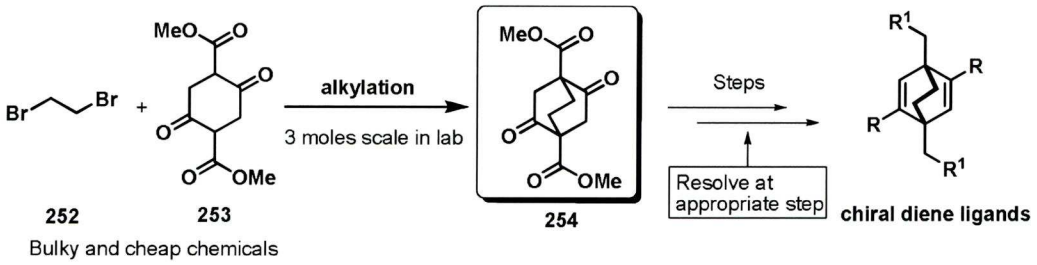
# Chapter 3 Chemoenzymatic synthesis of 1,4-disubstituted bicylco[2.2.2]octan-2,5-chiral dienes

## 3.1 Introduction.

As discussed earlier, chiral diene ligands have shown excellent catalytic performance both in reactivity and enantioselecitvity in various transformations. However, compared with phosphine ligands and $C_1$-symmetric dienes, the accessibility and structural variation in the most widely employed $C_2$-symmetric [2.2.2] diene ligands has been limited by inflexible synthetic routes and most notably the difficulty in resolution of the dienes or their synthetic precursors, which is currently achieved using chiral HPLC separation of the diene or a late stage intermediate [18, 37, 40, 49, 65, 99, 101, 104, 107, 110, 143, 148, 176].

It is of great importance to enrich the libraries of this unique kind of new ligands in a more efficient way. In addition, discovery of new ligands with higher efficiency would aid the understanding of the nature of this new group of ligands, which in turn would inform the development of new ligands with improved catalytic performance.

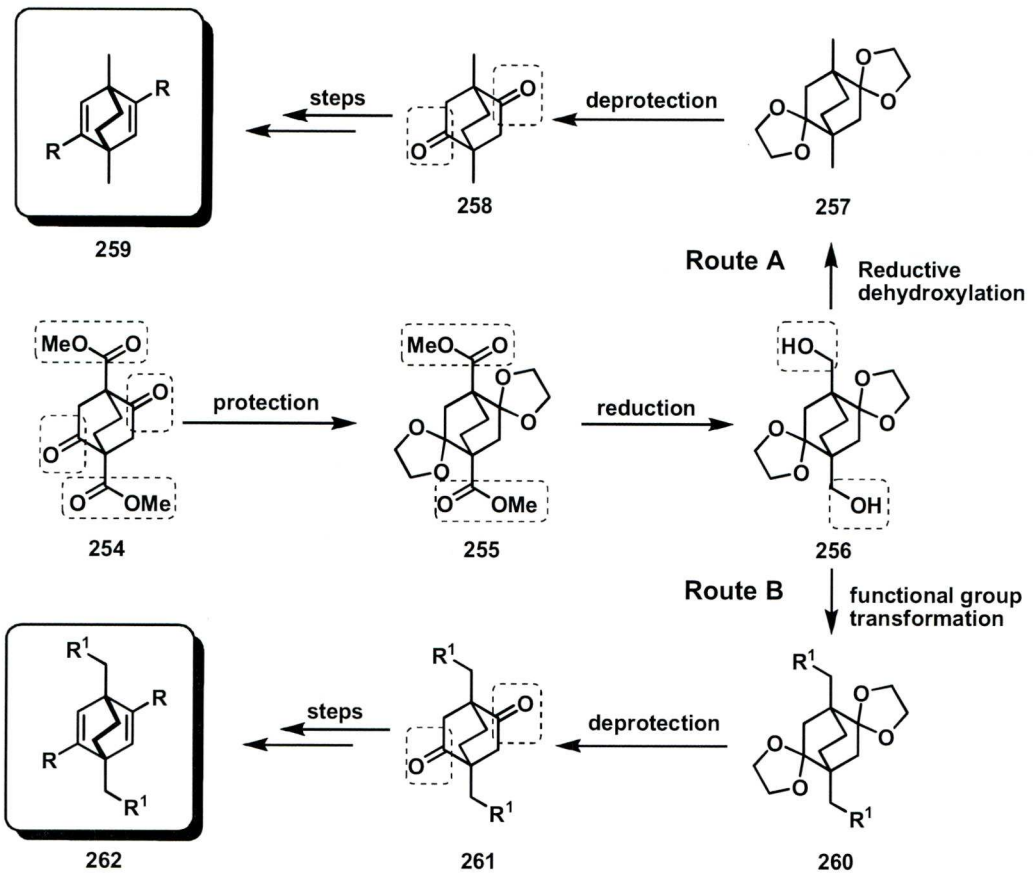
We were surprised to find that compound **254** had been synthesized some time ago [177], but it has never been used as a precursor for diene ligands. Due to the availability of the starting materials and the scalability of the preparation, we envisaged that compound **254** could provide a potential scaffold for diene ligands (***Scheme 3.1.1***).




***Scheme 3.1.1*** Potential scaffold for chiral diene ligands

According to the space differentiation model of the diene ligands elucidated by Hayashi, it is reasonable to assume that the substituents at 1 and 4-positions might

have a detrimental affect on the enantioselectivity if they are bulky enough.




***Scheme 3.1.2*** Synthetic route design for dienes based on 1,4-disubstituted [2.2.2]octan-2,5-dione. Circled functional groups are potentially usfeul for lipase resolutions.

Our initial route design is shown in ***Scheme 3.1.2***. Due to the possible detrimental affect from 1,4-substituted methyl ester groups on catalysis, we firstly decided to convert them to methyl groups according to a series functional group transformations to give 1,4-dimethyl bicylco[2.2.2]octan-2,5-dione **258**, which would then provide access to the corresponding diene ligands **259** using literature procedures (Route A in ***Scheme 3.1.2***). Alternatively, the hydroxyl groups in compound **256** could be converted into other functional groups to access 1,4-disubstituted chiral diene ligands **262** (Route B).

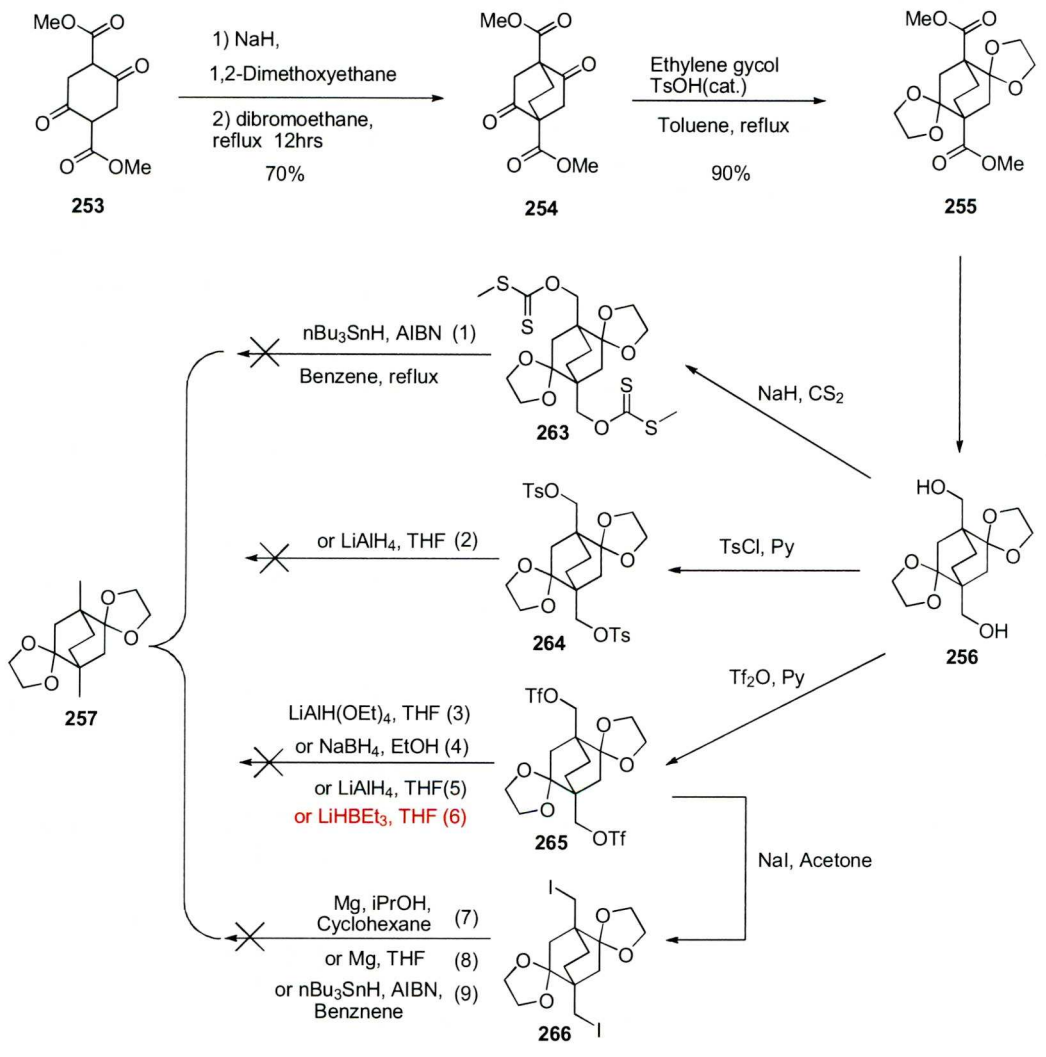
Besides the flexibility of the synthetic route, this approach also offers several choices

for enzymatic resolution: intermediates which have a ketone, ester, or hydroxyl group were all available for lipase resolution (compounds **254, 255, 256, 258** and **261**).

### 3.2 Results and discussion.

#### 3.2.1 Synthesis of 1,4-disubstituted bicyclic diketones

In order to prepare 1,4-dimethyl bicyclo[2.2.2]octan-2,5-dione **259** we explored the synthetic route outlined in ***Scheme 3.2.1***.




***Scheme 3.2.1*** Effort to synthesize 1,4-diemthyl bicyclo[2.2.2]octan-2,5-dione

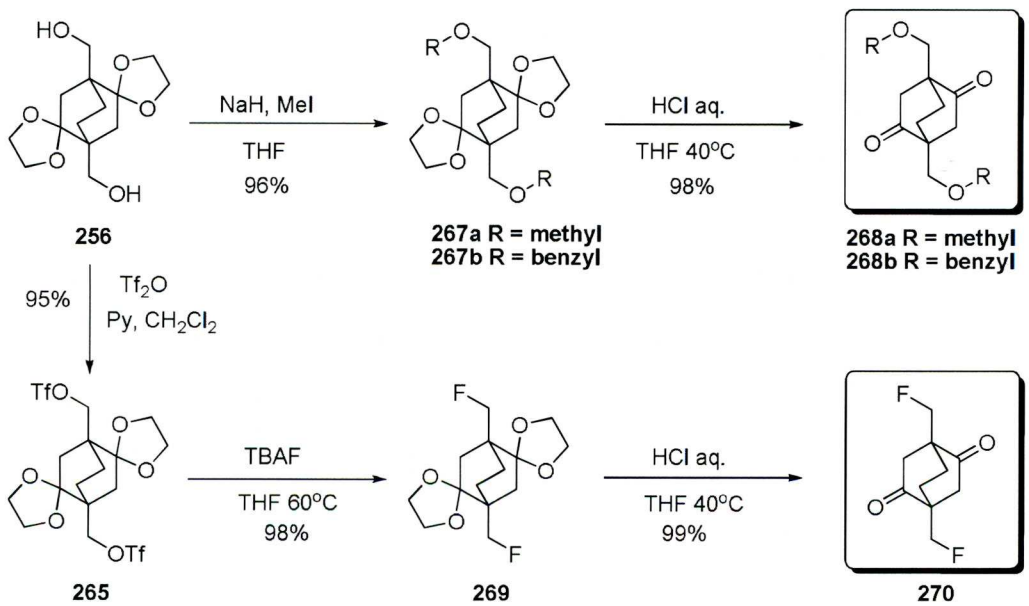
Starting from dimethyl succinylsuccinate **253**, the 1,4-di(methoxycarbonyl)-bicyclo[2.2.2]octan-2,5-dione **254** was synthesized in good yield. It was notable that a small modification to the literature procedure could improve both the reaction

efficiency and the yield. In the literature, 1,2-dimethoxyethane was chosen as solvent for the deprotonation of dimethyl succinylsuccinate by NaH and the deprotonation was fast and complete. Prior to the addition of 1,2-dichloroethane, most of 1,2-dimethoxyethane was removed and the resulting mixture was refluxed four days to give **254** in only 40% yield [178]. The long reaction time for the alkyaltion step may have been caused by the high solvation of the enolate by 1,2-dimethoxyethane. We tried less polar solvent such as toluene but found the deprotonation step became very difficult even upon heating. This may be attributed to the poor solubility of dimethyl succinylsuccinate in toluene. However, the reaction proceeded very slowly at room temperature. In an initially un-reacted and un-quenched experiment we found that the deprotonation was complete after about one month. We were then pleased to find that the following alkylation was very fast after 1,2-dibromoethane was added to this mixture and refluxed. Inspired by this result, a new strategy was used to improve the reaction. 1,2-Dimethoxyethane was still used as solvent to facilitate the deprotonation; then after the enolate had formed, the solvent was totally removed under reduced pressure to give a pink solid, which was further dried under vacuum overnight. The dry enolate was much more active than the solvated slurry: the subsequent alkylation step was then complete only after 12 hr and the pure product crystallized from the reaction mixture on cooling. The isolation was very straightforward: simple filtration to remove the solvent and aqueous washing to remove the NaBr and other water soluble salts afforded the pure product in 70% yield.

The ketone groups in compound **254** were converted into ketal **255** by reacting with ethylene glycol catalyzed by TsOH in 90% yield. The ketal **255** was reduced by $LiAlH_4$ to give diol **256** with 85% yield. However, the deoxygenation proved difficult to achieve. Initially, Barton-McCombie reaction [179-181] was used on the xanthate ester **263** derived from the diol **256** but no product was isolated, although the starting material was consumed. Ditosylate **264** was prepared in high yield and treated with lithium aluminum hydride [182] but no avail: at low temperature no reaction occurred, on heating all starting material decomposed. Then the more reactive

ditriflate **265** was tried with various hydride reagents. It was found that only super hydride (condition (6)) gave a trace amount of impure product, other conditions only consumed the starting material but yielded no product. Changing the leaving group to iodide (compound **266**) was attempted under several conditions but all failed, despite similarity to transformations in the literature [183, 184].

Having failed to synthesize the 1,4-dimethyl bicyclic diketone **258**, we turned to Route B. A new synthetic route was carried out as it shown in ***Scheme 3.2.2***. Starting from the diol **256**, 1,4- dimethoxymethyl or dibenzyloxymethyl bicylco[2.2.2]octan-2,5-dione **268a** and **268b** were obtained by alkylation followed by deprotection. Meanwhile the diol could undergo bistriflation, fluoro substitution and deprotection to give 1,4-di(fluoromethyl)-bicylco- [2.2.2]octan-2,5-dione **270**.

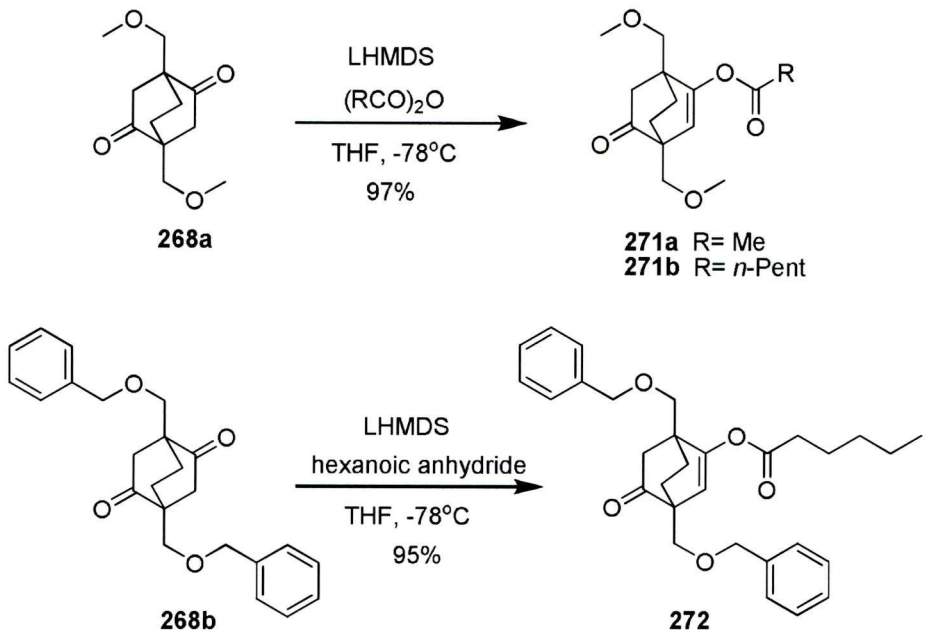



***Scheme 3.2.2*** Synthesis of 1,4-disubstituted bicyclic diketones

### 3.2.2 Resolution.

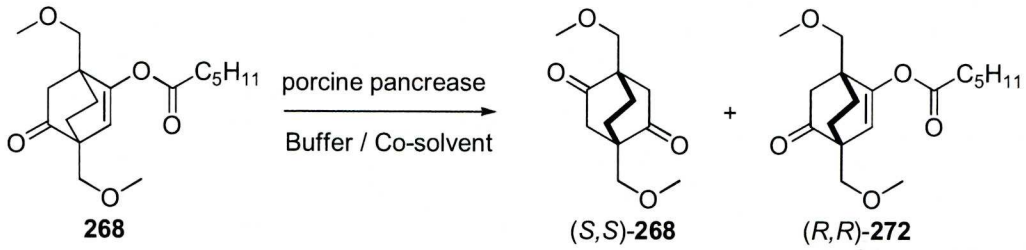
With these two bicyclic diketone scaffolds in hand, we investigated their resolution.

Firstly the enol acetate of **268a** was prepared (**Scheme 3.2.3**), however we found that the product shared the same Rf value as the starting material, leading to the difficulties in isolating the product even through the enzyme resolution was successful. A long chain ester was introduced to adjust the polarity.




***Scheme 3.2.3*** Synthesis of enol-ester as enzyme substrate

Compoud **271b** was subjected to lipase resolution. We screened various enzymes with little success. The only active enzyme was PPL (porcine pancreatic lipase), so we focused on this cheap enzyme. By adding a co-solvent to the buffer we were pleased to find that the enantiomeric ratio (E value) of the lipase increased markedly and reached a level acceptable for practical resolution (E = 25-50) (***Scheme 3.2.4***). Generally an E value of around 12 is the minimum for a kinetic resolution [185-187].



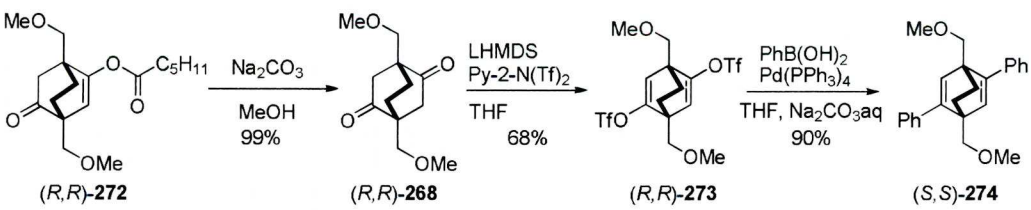

| Solvents[a]: | Buffer(neat) | DME | DMF | DMSO | $Et_2O$ |
|---|---|---|---|---|---|
| E Value: | 4-7 | 1 | 25-50 | 2 | ----- |

a) 100mg substrate, 4ml of buffer (if without co-solvent 5ml of buffer (0.1M NaPi, pH7.0) was used, 1ml co-solvent, 5%wt enzyme

***Scheme 3.2.4*** Kinetic resolution of **268** with the aid of co-solvents.

At the same time, due to the ease of cleavage of benzyl ethers, the enol hexanoyl ester of **268b** was made (compound **272**, ***Scheme 3.2.3***) and subjected to PPL but there was no selectivity for this substrate.

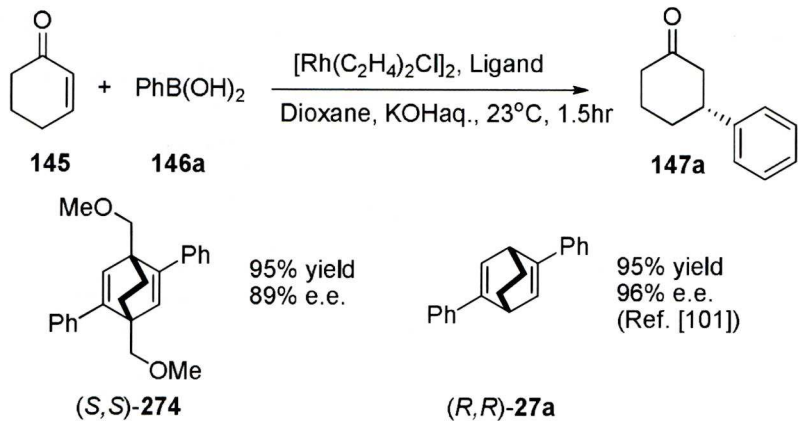
The reaction was scaled up and for 2.5g of enol hexanoate (+/-)-**272**, 500mg enantiomerically pure (*R,R*)-ester **272** was obtained (20% yield). This was converted into the corresponding diene ligand (*S,S*)-**274** *via* the synthetic route shown in ***Scheme 3.2.5***.




***Scheme 3.2.5*** Synthesis of 1,4-di(methoxymethyl)-2,5-diphenyl bicyclo[2.2.2]octan-2,5-diene

De-esterification of enol ester (*R,R*)-**272** gave diketone (*R,R*)-**268** in quantitative yield. The resulting diketone was subjected to literature procedures [101] to give the new 1,4-disubstituted diene ligand in good yield.

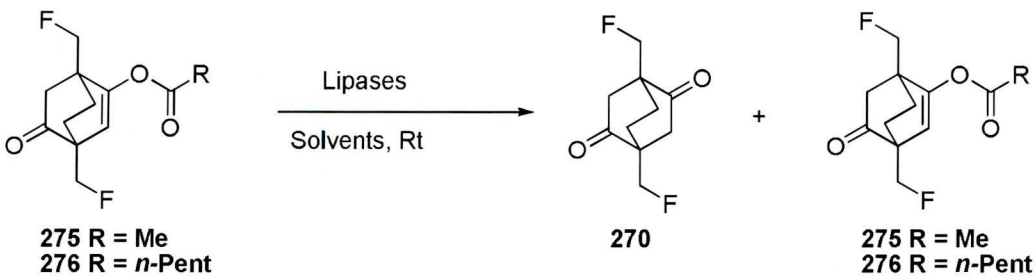
This ligand was tested in the asymmetric 1,4-conjugate addition of phenyl boronic acid with 2-cyclohexenone (***Scheme 3.2.6***). It gave excellent yield but the enantio-selectivity was lower than that gained using Hayashi's ligands 2,5-diphenyl bicylco[2.2.2]octan-2,5-diene (*R,R*)-**27a**.




***Scheme 3.2.6*** Conjugate addition catalyzed by 1,4-substituted chiral diene ligands

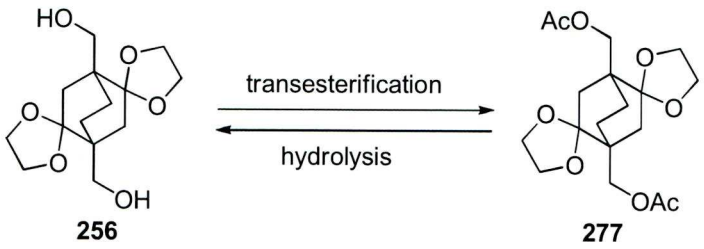
Comparing these two ligands, the only difference between (*S,S*)-**274** and (*R,R*)-**27a** is the 1,4 substitutent goups, and it is reasonable to attribute the lower enantioselectivity induced by ligand **274** to the presence of the methoxylmethyl group at the 1 and 4-positions.

This result prompted us to incorporate a smaller substituent at the bridge head positions , namely the fluoromethyl group (***Scheme 3.2.7***).




***Scheme 3.2.7*** Lipase-catalyzed kinetic resolution of the 1,4-di(fluoromethyl)substituted bicyclic enol ester **275** and **276**.

Unfortunately, we did not obtain a satisfactory resolution with either **275** or **276** despite intensive screening, which included varying the enzyme and solvent conditions.

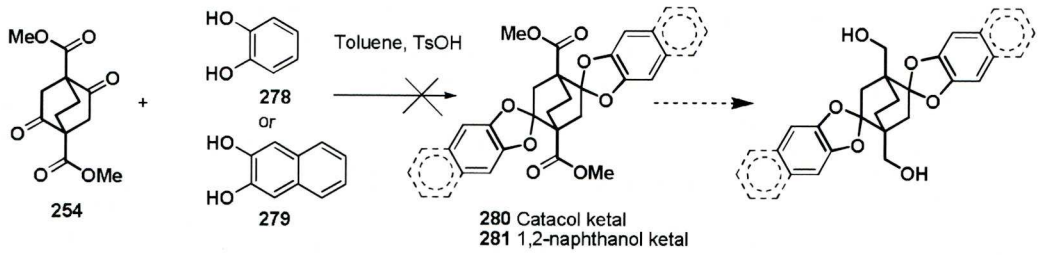



**256** **277**

***Scheme3.2.8*** Lipase-catalyzed resolution of 1,4-disubstituted bicylic [2.2.2] scaffold

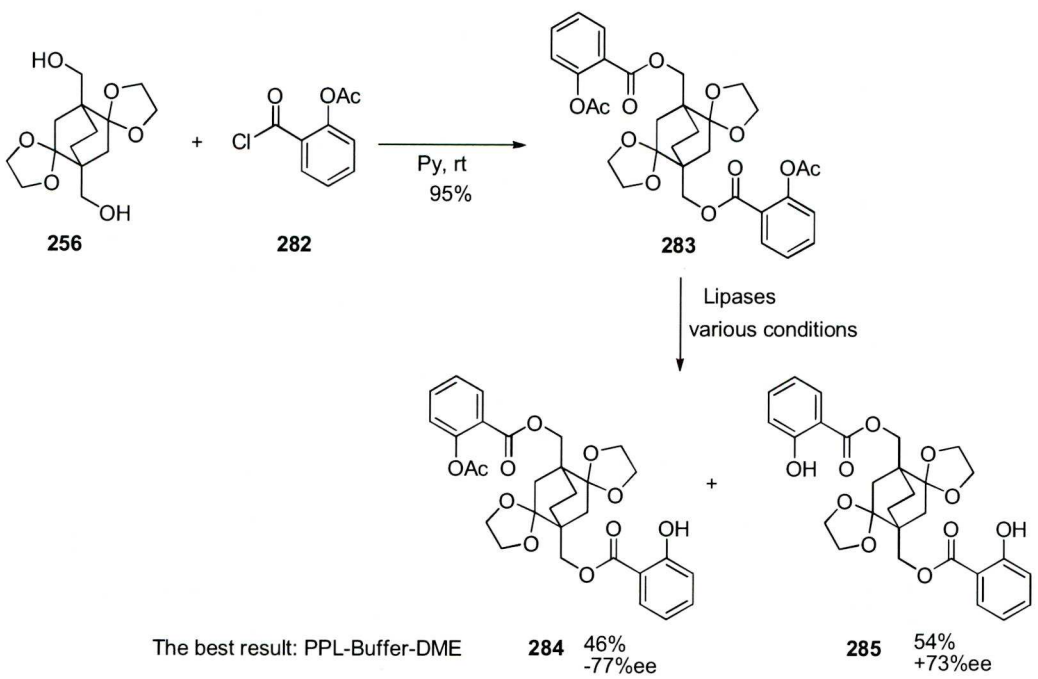
We also attempted to utilize the two hydroxyl groups in **256** for resolution. Starting from the diol **256**, the di-acetate **277** was also prepared for lipase resolution (***Scheme 3.2.8***). Both of the two substrates were subjected to lipase catalyzed hydrolysis or transesterification. Preliminary screening results suggested that some lipases had relatively high activity in hydrolysis or transesterification reactions, however difficulties associated with analysis proved to be prohibitive: the diacetate groups in **277** have a very weak UV absorbance making HPLC difficult.

The introduction of an UV chromophore was considered (***Scheme 3.2.9***). Initially, modification of the ketone groups at the 2,5-positions were considered. Both catechol **278** and 1,2-dinaphthanol **279** were used in an attempt to form ketals. Unfortunately both failed perhaps because of the rigidity of the diol groups in the aromatic ring.




***Scheme3.2.9*** preparation of substrates containg chromophor groups for lipase resolution

After failing to introduce chromophoric groups at the 2 and 5-positions, we changed strategies to investigate the 1 and 4-positions. From the perspective of facile formation and cleavage, the benzoyl ester of diol **256** was considered. Moreover, almost all lipases have high activity with acetyl esters, so an extra acetyl ester was introduced to the phenyl moiety. Acetylsalicylic ester **283** was designed and expected to yield a good resolution through hydrolysis of the acetyl groups in salicylic moiety (***Scheme 3.2.10***).

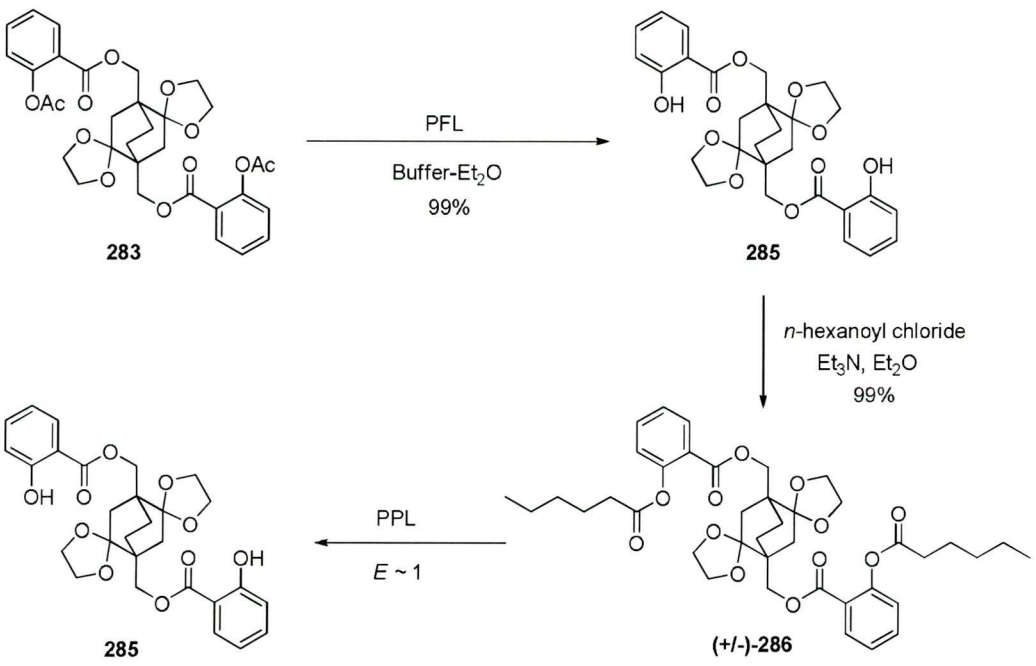



***Scheme3.2.10*** preparation of substrates containg chromophoric groups for lipase resolution

High throughput screening was carried out, and we found a moderately successful condition by using PPL in buffer-1,2-dimethoxyethane mixtures. Diacetate **283** was

hydrolyzed to bis-hydrolyzed product **285** (54%, +73% e.e.) and mono-hydrolyzed product **284** (46%, -77% e.e.). However, efforts to convert the enantiomerically enriched compound **284** to enantiomerically pure isomer failed, as the reaction proceeded the enantioselectivity dropped with the E value dropping to 1. The hydrolysis continued to proceed but the e.e. did not increase.

The acetyl groups of **283** were replaced by longer chain esters (**286**). By using PFL, diacetate **283** was completely converted into di-phenol compound **285**, which was easily be transformed into hexanoyl ester **286** by treatment with hexanoyl chloride and triethyl amine in diethyl ether. The bis hexanoyl ester **286** was subjected to lipase resolution (***Scheme 3.2.11***). It was found that only PPL showed good activity to this substrate, however it directly gave bis-hydrolyzed product without any enantioselectivity and monohydrolyzed product was not observed during the reaction.

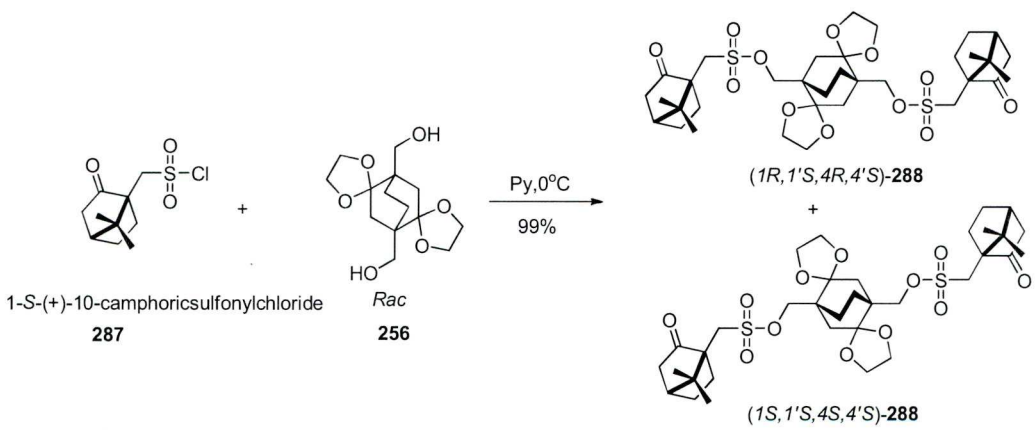



***Scheme 3.2.11*** Preparation of chromophor containing substrates for lipase resolution

### 3.2.3 Classical resolution:

We turned to traditional resolution in the hope of quickly obtaining some enantiomerically pure compound to allow us test the enantioselectivity of the ligands based on the new scaffold.

For ease of formation and cleavage, the OH groups at 1 and 4-positions were functionalized with a chiral auxiliary reagent (formation of chiral ketals of the 2,5-position ketone groups in compound **254** by using chiral diols such as *(S,S)*-1,2-diphenyl-ethylene glycol was tried but it was found that this kind of transformation was difficult, except for the ethylene glycol ketal). As shown in ***Scheme 3.2.12***, the (1*S*)-(+)-10-camphoricsulfonyl group was introduced to **256** to form a pair of diasteroisomeric esters (*1R,1S',4R,4S'*)-**288** and (*1S,1S',4S,4S'*)-**288**




***Scheme 3.2.12*** Preparation of diasteroisomers of compound **288**

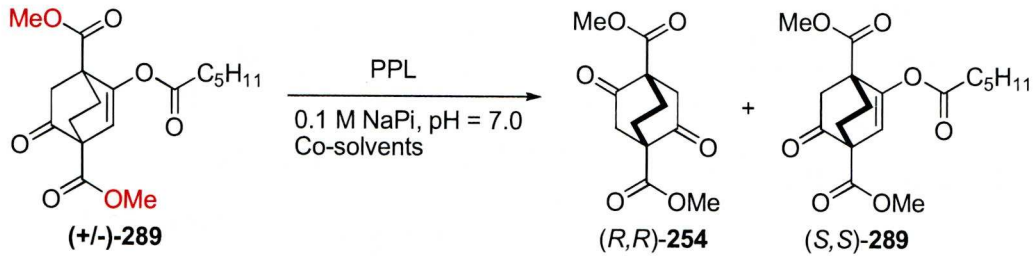
A crystalline product was formed but the two diastereoisomers could not be distinguished on TLC, and the proton NMR did not show obvious diasteroisomric peaks. Only carbon NMR indicated the presence of diasteroisomers. Fractional re-crystalliztions were carried out for this compound but there was no sign of resolution even after four recrystallizitons.

### 3.2.4 New strategy for enzymatic resolution

Considering the moderate selectivity obtained by PPL on the enol hexanoyl ester of 1,4-di(methoxymethyl) bicyclo[2.2.2]octan-2,5-dione **272**, we decided to focus our effort on the 1,4-di(methoxycarbonyl) bicylco[2.2.2]octan-2,5-dione **254**, which shared similar methoxy groups at the terminus of the 1 and 4-positions. This may be the crucial functional group for the PPL. In addition, we had tried to use the hydrolysis of the methyl ester in 1,4-di(methoxycarbonyl) bicylco[2.2.2]octan-2,5-dione but it did not work, which suggests that the methyl ester will not undergo competing hydrolysis in the presence of enzyme. As such, the enol hexanoyl ester of 1,4-di(methoxycarbonyl) bicyclo[2.2.]ocatn-2,5-dione **289** was prepared and subjected to PPL catalyzed kinetic resolution (***Table 3.2.1***).

Pleasingly, acceptable selective conditions were found by solvent screening. In biphasic ether-buffer solvent systems, such as *tert*-butylmethyl ether, diisopropyl ether or diethyl ether and buffer, the PPL has E values from 16- 20 (entries 2, 3 and 4). In the alkane-buffer system (entries 5 and 6), the reaction is too fast and the selectivity is quite low (when the reaction was stopped early to calculate the E value). In other polar solvents, there was no reaction (entries 7-10).

***Table 3.2.1*** Solvents screening for the resolution of compound **289**.



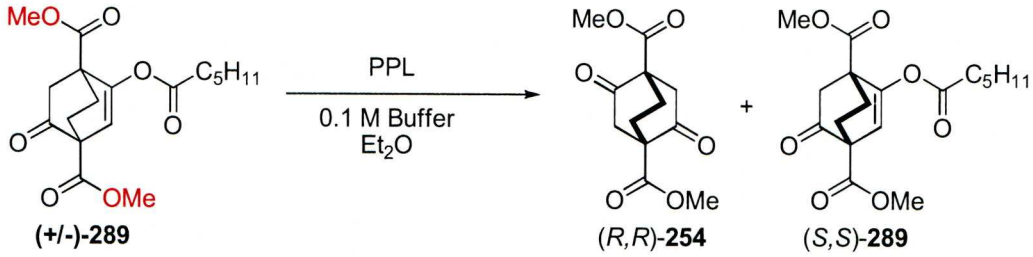

**(+/-)-289** (*R,R*)-**254** (*S,S*)-**289**

| Entry[a] | Solvent | conversion[b] | e.e.[c] | E-value |
|---|---|---|---|---|
| 1 | toluene | 0 | - | - |
| 2 | TBME | 39 | 54 | 20 |
| 3 | DIPE | 62 | 94 | 16 |
| 4 | $Et_2O$ | 51 | 84 | 20 |
| 5 | Pentane | 100 | - | - |
| 6 | Hexane | 80 | - | - |
| 7 | Pentanone | 0 | - | - |
| 8 | 3-methylpentylmethylketone | 0 | - | - |
| 9[d] | DME | 0 | - | - |
| 10[d] | DMF | 0 | - | - |

a) General conditions for each screen as follows: 10mgs substrate, 2mgs PPL, 2ml of organic solvent and 2ml buffer, stirring at rt. for 6hrs. b) conversion was determined by GC and calibrated by the ester **289** and ketone **254**. c) e.e was determined by chiral HPLC on Chiralpark AD column. d) 1ml of organic solvent and 4ml of buffer used.

It was also found that the pH value of the buffer affected the reaction greatly. The reaction goes to completion in 5hrs in $Et_2O$ and buffer with pH 7.5. A pH screen was carried out and the results suggested that this hydrolysis is very sensitive to the pH (***Table 3.2.2***). The best result was obtained at pH 5.2 for which the buffer is 0.1 M citric acid – tri sodium citrate.

***Table 3.2.2*** pH screening for the resolution of compound **289**.

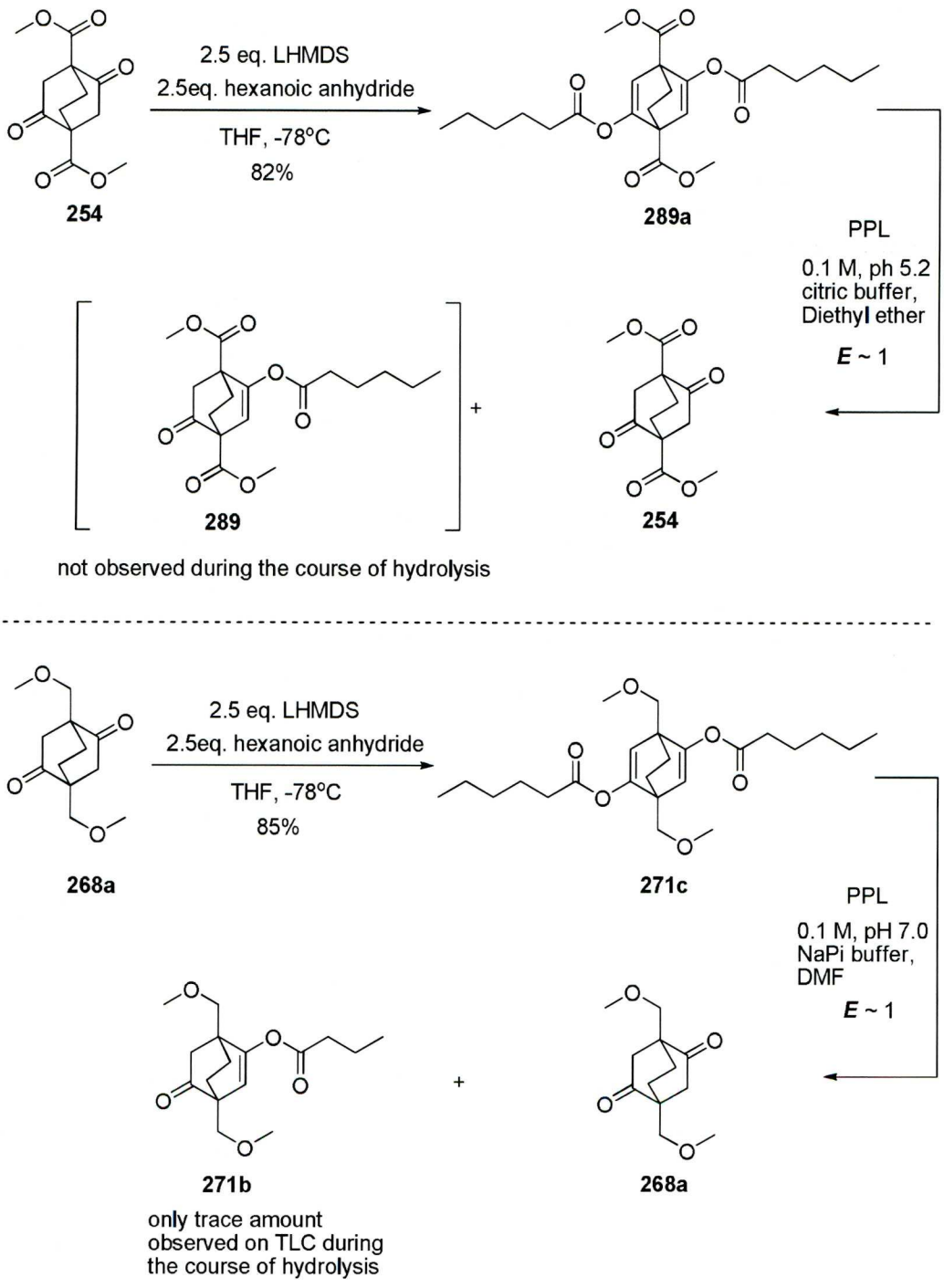



**(+/-)-289** (*R,R*)-**254** (*S,S*)-**289**

| Entry[a] | pH | conversion[b] | e.e.[c] | E-value |
|---|---|---|---|---|
| 1 | 6.8 | 60 | 91 | 7.5 |
| 2 | 6.6 | 47 | 74 | 21 |
| 3 | 6.4 | 50 | 82 | 27 |
| 4 | 6.2 | 49 | 54 | 6 |
| 5 | 6.0 | 52 | 84 | 21 |
| 6 | 6.2 | 27 | 34 | 27 |
| 7 | 5.2 | 41 | 64 | 60 |
| 8 | 5.0 | 43 | 61 | 8 |
| 9 | 4.8 | 31 | 38 | 17 |
| 10 | 4.4 | 30 | 38 | 24 |
| 11 | 4.0 | 0 | -- | -- |

a) In entries1-6, 0.1M NaPi buffer solution was used, and in entries 7-11, the buffer system was 0.1M citric acid-tri-sodium citrate. b) conversion was determined by GC and calibrated by the ester **289** and ketone **254**. c) e.e. was determined by chiral HPLC on Chiralpark AD column.

It's notable that in the scaled up synthesis of **289**, a small amount of side product which is highly sensitive to $KMnO_4$ staining was isolated and identified as the bis-enol hexanoyl ester **289a**, a compound we did not expect to obtain due to the failure in the attempted synthesis of bis-enol acetate **246**. So just by slightly optimization, bis-enol hexanoyl esters **289a** and **271c** were synthesized in good yield respectively (***Scheme 3.2.13***).




***Scheme 3.2.13*** Synthesis of bis-enol-ester as enzyme substrates

As we had established practical PPL-catalyzed kinetic resolution for each of the mono enol hexanoyl esters we wondered whether an enantioselectivity amplification would

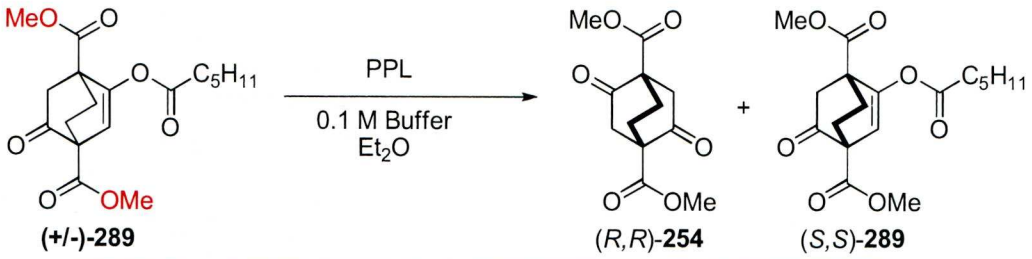
be obtained by starting from the bis enol esters due to their $C_2$ symmetry. However, the results are disappointing. Compared with the resolution with the mono enol esters, the bis enol esters were converted at a faster rate under the same conditions. However, unfortunately, for both of bis enol esters, the hydrolysis directly gave bis hydrolyzed products with no selectivity similar to the hydrolysis of bis hexanoyl ester **286**. There had been successful example reported in literature on the amplification of a $C_2$ symmtric compound. 1,1'-Bi-2-naphthol, a widely used scaffold for synthesis of chiral ligands, was resolved by a cholesterol esterase-catalyzed hydrolysis of 1,1'-bi-2-naphthyl pentanoate. The hydrolysis underwent a double highly enantioselective hydrolysis and as a result gave a very good resolution of (*S*)-1,1'-bi-2-naphthol and the (*R*)-1,1'-bi-2-naphthyl pentanoate without isolation of the intermediate 1,1'-bi-2-naphthol mono-pentanoate(mono hydrolyzed product) [188, 189].

### 3.2.5 Large scale resolution

Having found the optimum conditions, the resolution was scaled upon going from10mg scale to 1g, an increase in reaction rate was observed. Nevertheless, the substrate reached >99% e.e. with around 65% conversion. Surprisingly this reaction could not be reproduced when the scale was increased to 2g of substrate. The reaction stopped when the e.e. reached 95%. 3 and 10 gram scale batches were tried separately but the same result was obtained. The reaction stopped when the e.e. reached to around 95% (***Table 3.2.3***).

The kinetic profile of entry 4 in table 3.2-3 was determined and it can be clearly seen that the reaction was very fast over the first 24 hrs and slows down from 24 hrs to 48 hrs, where the e.e. and conversion were 92% and 51% respectively. After 48hrs, over the following 3 days, the reaction almost stopped (***Fig 3.2.1***).

***Table 3.2.3*** Scale-up experiments for the kinetic resoluion




**(+/-)-289** (*R,R*)-**254** (*S,S*)-**289**

| Entry | substrate amount (gram) | reaction time ( day ) | conversion[a] | ee[b] |
|---|---|---|---|---|
| 1 | 1 | 6 | 69 | 99.6 |
| 2 | 2 | 8 | 52 | 95 |
| 3 | 3 | 5 | 51 | 92 |
| 4 | 10 | 5 | 60 | 95 |

a) conversion was determined by GC and calibrated by the ester **289** and ketone **254**. b) e.e was determined by chiral HPLC

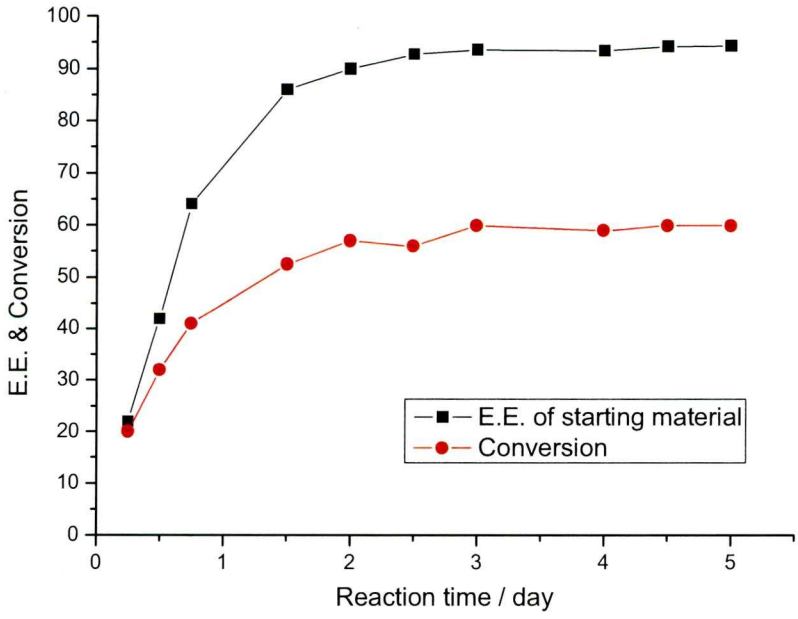



***Fig 3.2.1*** Kinetic profile for the PPL catalyzed resolution (based on 10 gram scale)

At first the monitoring pH value was considered. However, the pH value did not change as the reaction proceeded; adjusting the pH to 7.0 did not change the reaction

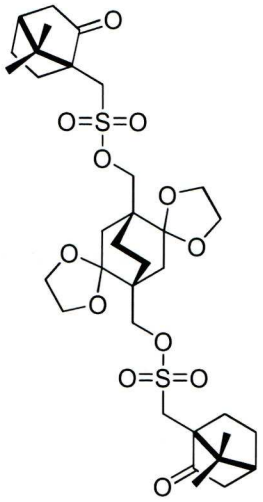
problem. Isolating the organic layer and washing off the hexanoic acid by using NaOH solution before subjecting the ethereal solution to a fresh buffer with new enzyme also did not affect the reaction.

An alternative strategy was chosen in order to rectify this problem. We hoped that the enantiomerically riched enol hexanoate could be promoted to >99% e.e. by re-crystallization. We were pleased to find that this method worked successfully. The minor enantiomer co-crystallized with the antipodal enantiomer in 1:1 ratio, so as a result a near theoretical isolation of pure enantiomer was obtained: i.e., the enol hexanoate with 95% e.e. could be improved to >99% e.e. with 94% yield, while the e.e. of the crystals (5% yield) was about 0%.

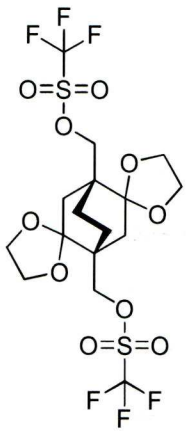
The resolution was carried out at large scale varying between 10 to 40 grams of starting (+/-)-ester. The reaction was stopped when it reached the inhibititon point. The enantiomerically enriched enol hexanoate was purified by recrystallization in Hexane-EtOAc. 25-30% final yield of the enantiomerically pure isomer could be obtained (yield calculated based on the mass of the racemic compound). The antipodal enantiomer, which had been hydrolyzed into corresponding diketone **254**, could also be purified in this way after being converted back to the enol hexanoate by treatment with LHMDS and hexanoyl anhydride (20-28% yield).

### 3.2.6 Determination of the absolute configuration.

We had attempted chemical resolution of the diol **256** by introducing the camphor sulfonyl groups into the 1 and 4-positons. Although unsuccessful, the mixed diasteroisomers were highly crystalline. The single enantiomer of (*S,S*)-**289** obtained was converted into its bis camphor sulfonyl ester ((1*S*,1'*S*,4*S*,4'*S*)-**288**, ***Scheme 3.2.13***) and subject to re-crystalliztion for the purpose of determination of absolute configuration.



(*1S,1'S,4S,4'S*)-**288**



(*1S,4S*)-**265**

***Scheme 3.2.13*** Compounds for determining absolute configuration

We were surprised to find that optically pure sulfonyl ester became very difficult to crystallize, giving an amorphorous powder or sticky oil, despite the use of various of solvents. This phenomenon perhaps explains why classical resolution of this kind of bicyclic scaffold is so difficult. Finally and fortunately the absolute configuration was determined by single crystal diffraction on the intermediate (1*S*,4*S*)-**265** (***Scheme 3.2.13*** and ***Fig 3.2.2***), which appears as fine needle type crystal after being recrystallized from hexane-EtOAc. The absolute configuration of the enol hexanoate which the enzyme disfavored was therefore (*S,S*).

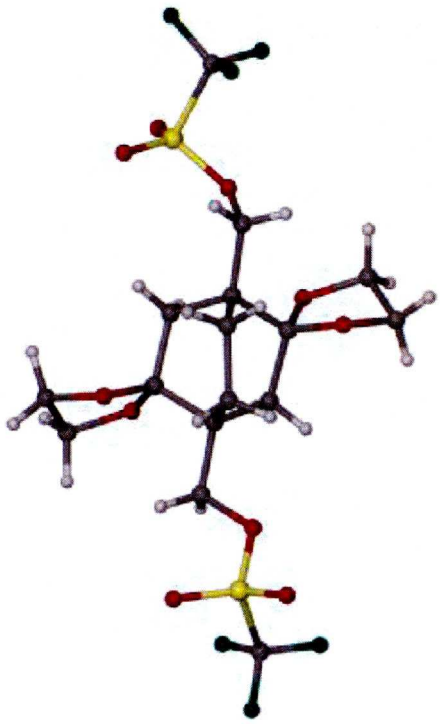
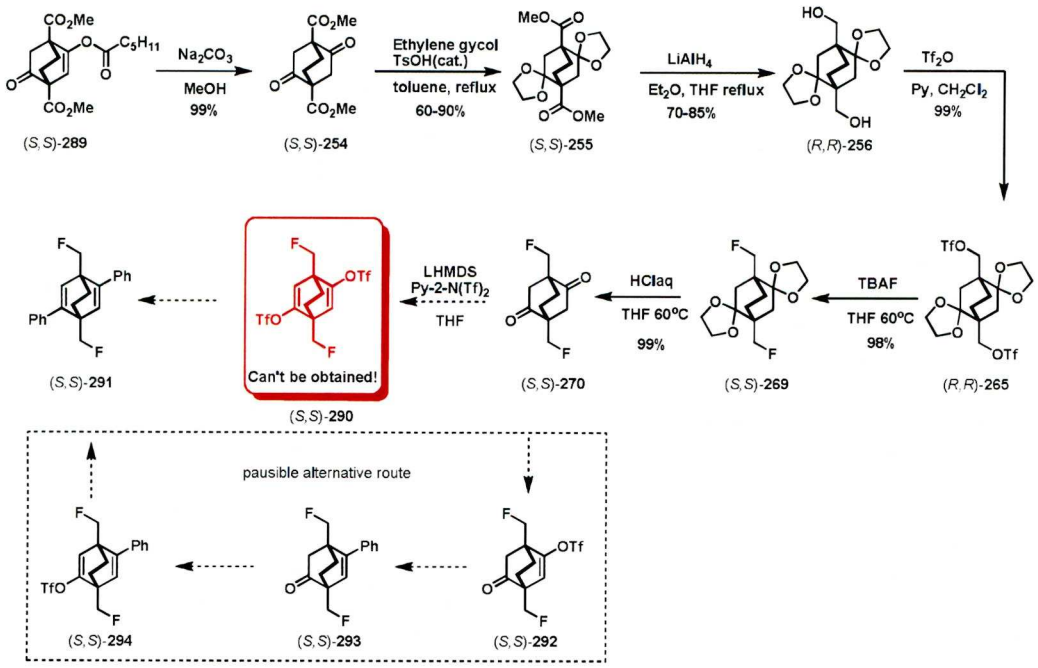
| ***Crystal and Refinement Data*** | |
|---|---|
| $C_{16}H_{20}F_6O_{10}S_2$<br>$M = 550.44$<br>yellow prism, 0.50 × 0.40 × 0.30 $mm^3$<br>orthorhombic, $P2_12_12_1$ (No. 19)<br>$a = 5.9914(5)$ Å<br>$b = 18.001(2)$ Å<br>$c = 19.852(2)$ Å<br>$V = 2141.1(3)$ $Å^3$,<br>$Z = 4$,<br>$D_c = 1.708$ $g/cm^3$<br>$T = 100(2)$K<br>MoKα radiation, $\lambda = 0.71073$ Å,<br>$2\theta_{max} = 54.9°$<br>12789 reflections collected, 4731 unique<br>$R_{int} = 0.0271$<br>Final *GooF* = 1.137<br>*R1* = 0.0362, *R2* = 0.0765<br>387 parameters, 0 restraints<br>Absolute structure parameter = 0.0(1)<br>$\mu = 0.095$ $mm^{-1}$ |  |

***Fig3.2.2*** Molecular structure obtained from X-ray single crystal diffraction of compound (*1S,4S*)-**265**.

### 3.2.7 Efforts towards the synthesis of the 1,4-di(fluoromethyl)-substituted bicyclic [2.2.2] chiral diene ligand

According to the route we designed initially, starting from enantiomerically pure (*S,S*)-**289**, 1,4-di(fluoromethyl)substituted bicylic diketone (*R,R*)-**270** (precursor to 1,4-di(fluoromethyl)-2,5-diphenyl bicyclo[2.2.2]octa-2,5-diene) was prepared smoothly *via* a high yielding route (***Scheme 3.2.14***). Methanolysis of enol hexanoate (*S,S*)-**289** gave diketone (*S,S*)-**254**, which underwent bisketalization and reduction sequentially to give diol (*R,R*)-**256**. The OH groups in the diol (*R,R*)-**256** were converted into fluoro groups by triflation followed by fluoride substitution. Finally deketalization afforded the 1,4-di(fluoromethyl)- diketone (*S,S*)-**270**.




***Scheme 3.2.14*** effort for the synthesis of 1,4-di-fluoromethyl-2,5-diphenyl bocyclo[2.2.2]octan-2,5-diene

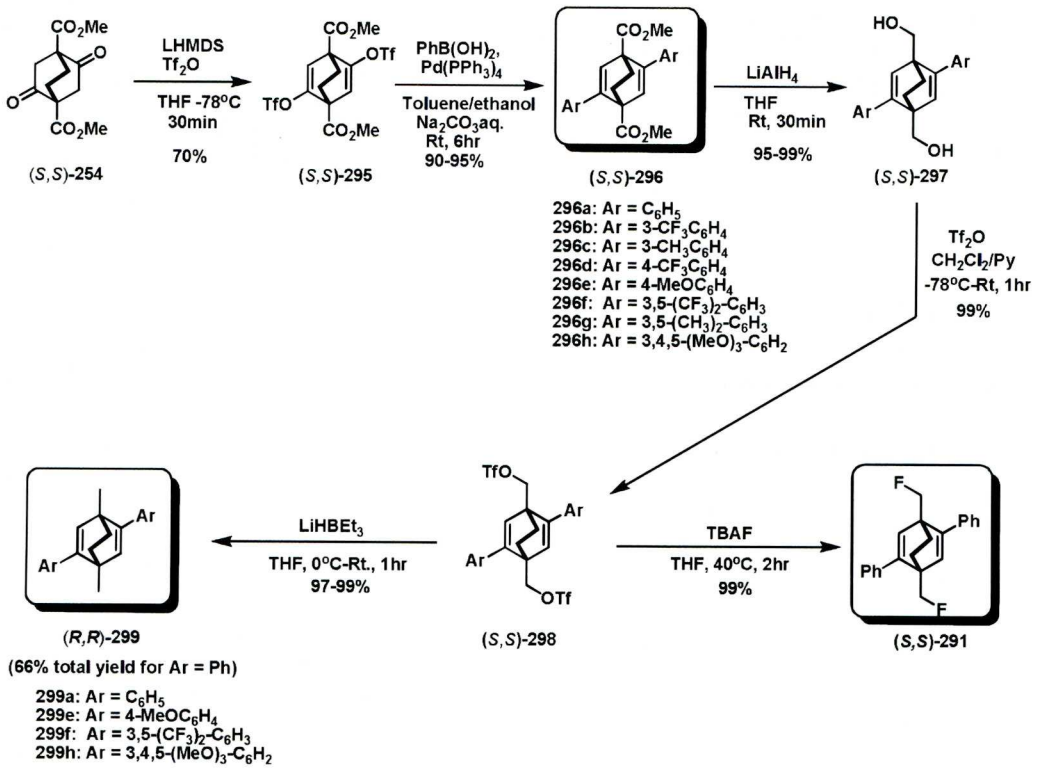
To our disappointment, synthesis of the bis enol triflate of the diketone (*S,S*)-**290** failed, and we were unable to directly access to chiral diene ligand (*S,S*)-**291**. The bisenoltriflation shared the same problem as encountered in the synthesis of bis enol acetate **246** (page 62, ***Scheme 2.2.4***, chapter 2). The only product obtained was the

mono enol triflate (*S,S*)-**292** regardless of how many equivalents of base and Comin's reagent [190-192] were added. A sequential arylation might be a plausible alternative route to access the final diene ligand (*S,S*)-**291**. However, this would considerably lengthen the synthetic route. Therefore we decided to investigate other ideas before resorting to this sequential process.

### 3.2.8 Synthesis of 1,4-disubstituted bicylco [2.2.2] chiral diene ligands

A new strategy was considered since the double enol triflation was a problem. We decided to introduce the aryl groups at the 2 and 5 positions prior to modifying the 1 and 4 positions (***Scheme 3.2.15***). We were very pleased that this strategy worked, which not only shortened the synthetic route and provided 1,4-di-(fluoromethyl)-2,5-diphenyl bicylo[2.2.2]octa-2,5-diene ligand with high yield. We were also able to access our original ideal ligand: 1,4-dimethyl-2,5-diphenyl bicyclo[2.2.2]octa-2,5-diene (**299**).

Starting from enantiopure dione (*S,S*)-**254**, formation of the bis-enol triflate was followed by introduction of the aryl substituents by palladium-catalysed cross-coupling to give ligands (*S,S*)-**296a-h** [69, 101, 193]. Lithium aluminium hydride reduction followed by bis triflation gave the ditriflate **298a, 298e, 298f** and **298h**. It was pleasing to find that without the ketals at the 2 and 5-positions, the ditriflate **298** could also undergo reductive detriflation with superhydride [194] giving (*R,R*)-ligands **299a, 299e, 299f** and **299h**. In addition, ditriflate group of **298a** could be displaced by fluoride ion gave the difluoro ligand **291**.




***Scheme3.2.15*** Synthesis of 1,4-disubstituted-2,5-diaryl- bicyclo[2.2.2]octan-2,5-dienes

## 3.3 Summary

We were developed a chemoenzymatic approach giving access to a new series of chiral 1,4-disubstituted $C_2$-symmetric [2.2.2] diene ligands (***Scheme 3.2.15***).

The scalability and ease of operation of the key enzyme resolution step, in addition to high yielding chemical transformations, provides a highly practical route that could quickly satisfy demands for greater quantities. Moreover, a significant electronic effect was observed in the diene ligands for rhodium-catalyzed arylation reactions. Both catalytic activity and enantioselectivity depends on the electronic properties of the ligands, which will be addressed in the next chapter.

# Chapter 4 Rh-diene-catalyzed asymmetric reactions

## 4.1 Introduction

Chiral dienes are a new class of highly effective ligands, developed independently by Hayashi and Carriera, that have shown great promise in the field of asymmetric catalysis for reactions catalysed by rhodium and iridium [18, 37, 195]. A range of synthetically useful transformations have been realized in excellent yield and enantiomeric excess using $C_1$-symmetric and $C_2$-symmetric dienes [40, 41, 44, 47-50, 59, 65, 68, 69, 99, 101-104, 107, 110, 120, 121, 131, 132, 137, 143, 148].

However, compared with phosphine ligands and $C_1$-symmetric dienes, the accessibility and structural variation in the most widely employed $C_2$-symmetric [2.2.2] diene ligands has been limited by inflexible synthetic routes and most notably the difficulty in resolution of the dienes or their synthetic precursors, which is currently achieved using chiral HPLC separation of the diene or a late stage intermediate [18], [40, 44, 49, 65, 99, 101, 104, 107, 110, 143, 148], [42, 150, 153, 158, 161]. As a result, the electronic effects on activity and enantioselectivity in these ligands have not been well studied. Although structural modifications including both electronic and steric changes have been made with the current bicyclic frameworks [50, 69, 101, 102, 107], the results have shown that steric factors are dominant. Hayashi has shown that $C_1$-symmetric [2.2.2] dienes can be electronically tuned to give excellent activity and selectivity for asymmetric arylation of *N*-nosylimines [50]. In this example it is believed that an electron withdrawing naphthyl ester substituent on one of the alkenes accelerates transmetallation to form a *trans* aryl-rhodium bond. The imine then coordinates at the vacant coordination site near to the sterically demanding naphthyl group giving high facial selectivity (***Scheme 1.4.3***., Chapter 1).

Although the chiral diene-Rh catalyst allows reactions to be conducted at lower temperatures compared with phosphine ligands, in diene-rhodium-catalyzed arylations with aryl boronic acids generally more than two equivalents of the arylboronic acid are necessary in order to achieve a high yield and for particularly inactive substrates

as many as 5eq. [78-80, 143]. This is attributed to the competing protodeboronation side-reaction [90-95, 196, 197] and indicates that reaction temperature is not the only factor responsible for the low atom efficiency in this case.

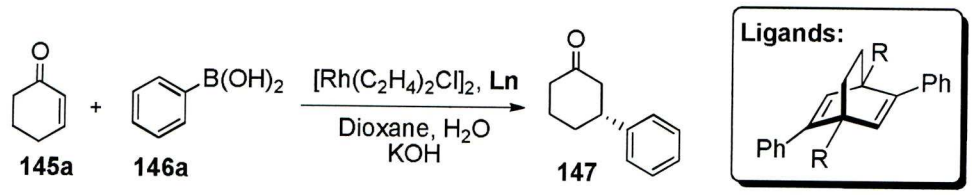
As discussed in Chapter 3, we have established a reliable, high yielding and practical synthetic route, providing access to a new series of chiral 1,4-disubstituted $C_2$-symmetric [2.2.2] diene ligands with a lipase-catalyzed kinetic resolution as the key step. This new scaffold can be easily modified and allows greater structural diversity than other [2.2.2] systems. What follows is an evaluation of the performance of catalysts formed from these new chiral dienes and Rh. To our great pleasure, a significant electronic effect was observed in the diene ligands for rhodium-catalyzed arylation reactions. Both catalytic activity and, more interestingly from a mechanistic perspective, enantioselectivity depend on the electronic properties of the ligands. In addition, atom efficiency for the aryl boronic acids was correlated.

## 4.2 Results and discussion

### 4.2.1 Conjugate addition to enones

Initially a small library of ligands with various functional groups at the 1,4-positons were evaluated for the asymmetric conjugate addition of phenylboronic acid **146a** to cyclohexenone **145a** using previously reported conditions (***Table 4.2.1***) [101, 102].

***Table 4.2.1*** Ligand screen for asymmetric conjugate addition to **145a**




| Entry[a] | Ln | Ligand 1,4-R | Ligand 2,5- Aryl | Yield[b] | e.e. of (*R*)-147[c] |
|---|---|---|---|---|---|
| 1 | (*S,S*)-296a | $CO_2Me$ | Ph | 95 | 89 |
| 2 | (*S,S*)-287a | $CH_2OH$ | Ph | 94 | 97 |
| 3 | (*S,S*)-274 | $CH_2OMe$ | Ph | 95 | 88 |
| 4 | (*R,R*)-299a | Me | Ph | 96 | 98 |
| 5[d] | (*R,R*)-299a | Me | Ph | 98 | 99 |
| 6 | (*S,S*)-291 | $CH_2F$ | Ph | 96 | 98 |
| 7[e] | (*R,R*)-27a | H | Ph | 97 | 96 |

[a] Reaction conditions: **145** (0.5mmol), **146a** (0.6mmol for **294a**, 1.0 mmol for the other ligands), [{$Rh(CH_2CH_2)_2Cl$}$_2$] (1.5mol% Rh), Ligand **Ln** (1.65 mol%), KOH (0.2 mmol) in dioxane/$H_2O$; 10:1 (2.3ml) at room temperature, 1hr for **294a** and 30°C, 3hr for the rest. [b] Yield of isolated product. [c] E.e.'s were determined by chiral HPLC on Chiralcel OD-H column. [d] As in [a] except MeOH/$CH_2Cl_2$; 10:1 (2.3ml), KOH (1.65mol%). [e] see ref. [101]

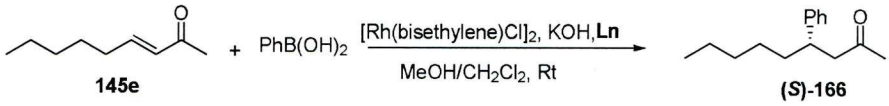
We found that substituent groups do affect the enantioslectivity. Except for ligands (*S,S*)-**296a** (89% e.e., R = $CO_2Me$, entry 1) and (*S,S*)-**274** (88% e.e., R = $CH_2OMe$, entry 3), ligands (*S,S*)-**287** (R= $CH_2OH$), (*R,R*)-**294a** (R = Me), and (*S,S*)-**291** (R = $CH_2F$) gave the product (*R*)-3-phenylcyclohexanone **147** in excellent yields and >97% e.e. which compares favorably with the previously reported 1,4-unsubstituted diene (*R,R*)-**27a** (entry 7) [101]. These results suggest that increased steric demands in the 1,4-position undermines the enantioselectivity (eg. the methoxy group present in both ester ((*S,S*)-**296a**) and ether ((*S,S*)-**274**)groups). Optimum selectivity was

achieved when using ligand (*R,R*)-**299a** in MeOH/$CH_2Cl_2$ (10:1) (entry 5) [103] rather than dioxane/water.

However, to our great surprise, the (*R,R*)-**299a** gave unexpectedly low enantioselectivity for 3-nonen-2one **145e** (entry 13, ***Table 4.2.2***) compared to that obtained for 2-cyclohexenone **145a**. Apart from the contrast in the enantioselectivity with (*R,R*)-**299a**, both 3-nonen-2-one and 2-cyclohexenone underwent arylation in excellent yield.

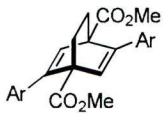
A systematic screening of ligands toward this substrate was carried out, and the results are shown in ***Table 4.2.2***.

***Table 4.2.2*** Ligand screen for asymmetric conjugate addition to **145e**

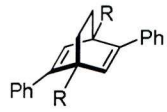



**145e** **(*S*)-166**

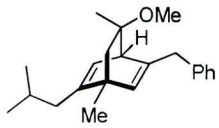
**Ligands**



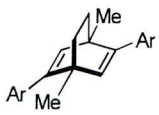
(*S*,*S*)-**296a:** Ar = Ph
(*S*,*S*)-**296b:** Ar = 3-$CF_3C_6H_4$
(*S*,*S*)-**296c:** Ar = 3-$CH_3C_6H_4$
(*S*,*S*)-**296d:** Ar = 4-$CF_3C_6H_4$
(*S*,*S*)-**296e:** Ar = 4-$MeOC_6H_4$
(*S*,*S*)-**296f:** Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*,*S*)-**296g:** Ar = 3,5-$(CH_3)_2C_6H_3$
(*S*,*S*)-**296h:** Ar = 3,4,5-$(MeO)_3C_6H_2$



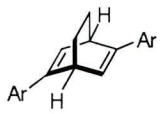
(*S*,*S*)-**287a:** R = $CH_2OH$
(*S*,*S*)-**291:** R = $CH_2F$
(*S*,*S*)-**274:** R = $CH_2OMe$



(*R*,*R*)-**29**



(*R*,*R*)-**299a:** Ar = Ph
(*R*,*R*)-**299f:** Ar = 3,5-$(CF_3)_2C_6H_3$
(*R*,*R*)-**299h:** Ar = 3,4,5-$(MeO)_3C_6H_2$

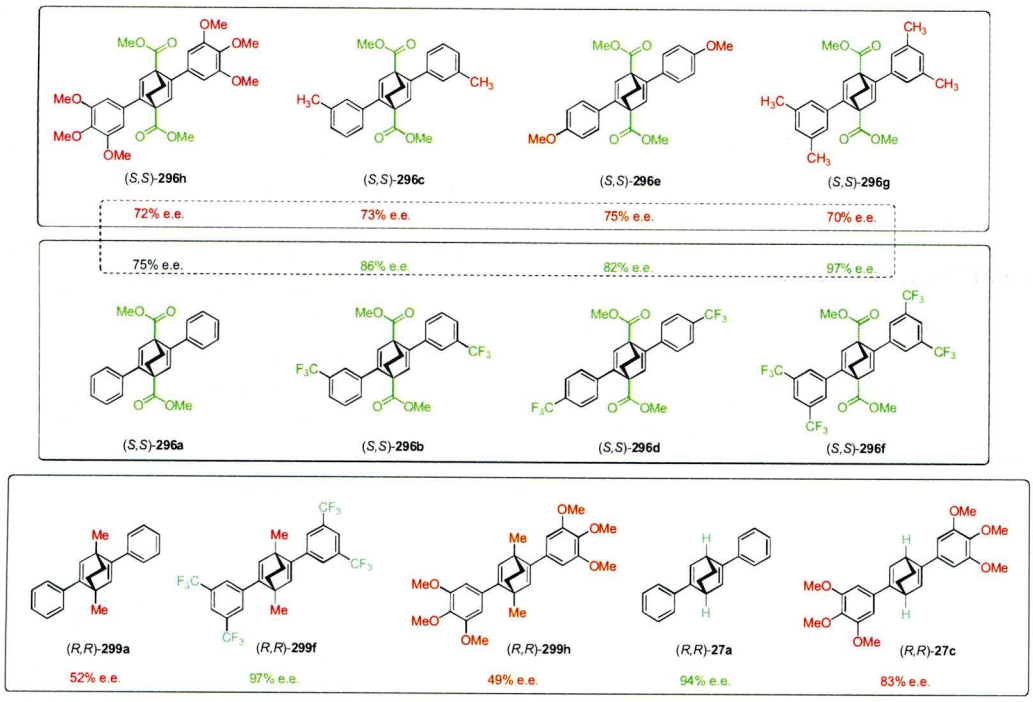


(*R*,*R*)-**27a:** Ar = Ph
(*R*,*R*)-**27b:** Ar = 4-$(MeOCO)C_6H_4$
(*R*,*R*)-**27d:** Ar = 3,4,5-$(MeO)_3C_6H_2$
(*R*,*R*)-**27e:** Ar = 2-$(CHO)C_6H_4$

| Entry[a] | Ln | Ligand 1,4-R | Ligand 2,5- Aryl | Yield[b] | e.e. of (*S*)-**166**[c] | δ[d] of Olefin $^1$H |
|---|---|---|---|---|---|---|
| 1 | **296a** | $CO_2Me$ | Ph | 95 | 75 | 6.64 |
| 2 | **296b** | $CO_2Me$ | 3-$CF_3C_6H_4$ | 92 | 86 | 6.76 |
| 3 | **296c** | $CO_2Me$ | 3-$CH_3C_6H_4$ | 98 | 73 | 6.62 |
| 4 | **296d** | $CO_2Me$ | 4-$CF_3C_6H_4$ | 95 | 82 | 6.74 |
| 5 | **296e** | $CO_2Me$ | 4-$MeOC_6H_4$ | 99 | 75 | 6.56 |
| 6 | **296h** | $CO_2Me$ | 3,4,5-$(MeO)_3C_6H_2$ | 98 | 72 | 6.40 |
| 7 | **296f** | $CO_2Me$ | 3,5- $(CF_3)_2C_6H_3$ | 95 | 97 | 6.89 |
| 8 | **296g** | $CO_2Me$ | 3,5- $(CH_3)_2C_6H_3$ | 96 | 70 | 6.52 |
| 9 | **287a** | $CH_2OH$ | Ph | 98 | 67 | 6.27 |
| 10 | **274** | $CH_2OMe$ | Ph | 98 | 57 | 6.25 |
| 11 | **291** | $CH_2F$ | Ph | 95 | 71 | 6.30 |
| 12 | **29** | H, Me | *i*-Pr, Bn | 99 | 94 | 5.71;5.64 |
| 13 | **299a** | Me | Ph | 99 | 52 | 5.97 |
| 14 | **299f** | **Me** | **3,5- $(CF_3)_2C_6H_3$** | **99** | **97** | **6.07** |
| 15 | **299h** | **Me** | **3,4,5-$(MeO)_3C_6H_2$** | **99** | **49** | **5.99** |
| 16[e] | **27a** | H | Ph | 95 | 94 | 6.63 |
| 17 | **27c** | H | 4-$(MeOCO)C_6H_4$ | 99 | 92 | 6.79 |
| 18 | **27d** | H | 3,4,5-$(MeO)_3C_6H_2$ | 98 | 83 | 6.59 |
| 19 | **27e** | H | 2-(CHO)- $C_6H_4$ | N.R. | -- | 6.36 |

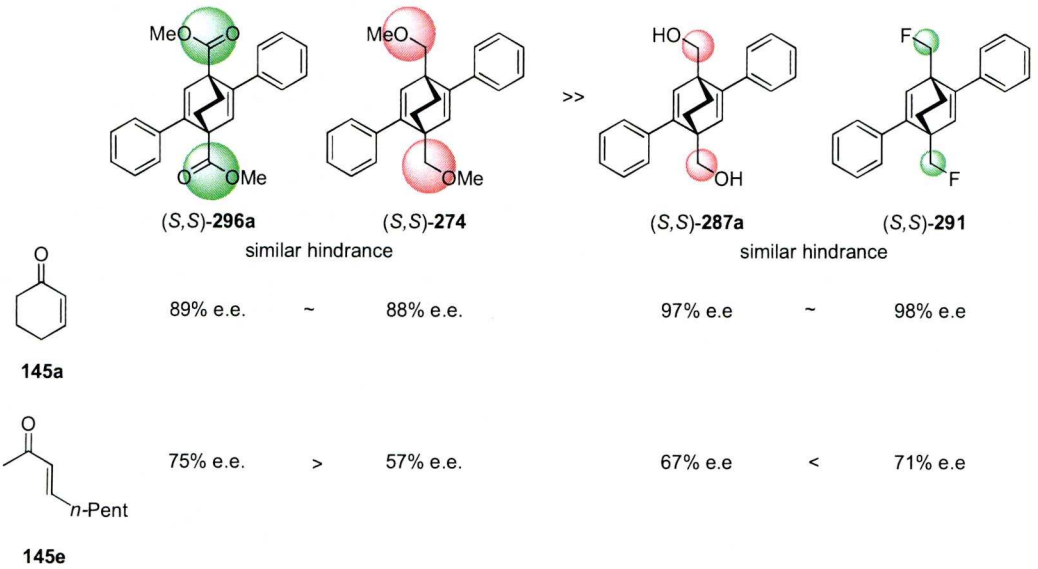
[a] Reaction conditions: **145e** (0.3mmol), **146a** (0.6 mmol), [{$Rh(CH_2CH_2)_2Cl$}$_2$] (3mol% Rh), Ligand **Ln** (1.65 mol%), KOH (0.15 mmol) in dioxane / $H_2O$; 10 :1 (1ml dioxane and 0.1ml $H_2O$) at room temperature, 3hr at 30°C. [b] Yield of isolated product. [c] E.e.'s were determined by chiral HPLC after converting **166** to methyl-addition-to-ketone derivertive (see experiment sections, Chapter 5). [d] δ was recorded as ppm from the $^1$H NMR (400MHz, $CDCl_3$) spectrum of each ligand. [e] ref. [101]

Initially, a series of 1,4-methoxycarbonyl-substituted ligands were tried. The results from entries 1-6 for enantioselectivity were not as good as other [2.2.2] bicyclic ligands in the literature [40, 48, 102, 143]. From a purely structural perspective, it was logical that the substituent ester groups at the 1 and 4- positions may be detrimental to the enantioselectivity (the results using (*S,S*)-**296a** with 2-cylcohexenone also supports this assumption (entry 1, ***Table4.2.1***)). However, comparison of the results for (*R,R*)-**296a** and (*R,R*)-**299a** show that the 1,4-diester ligand (*S,S*)-**296a** out-performs the 1,4-dimethyl ligand (*R,R*)-**299a** significantly. Similar results were obtained with another acyclic enone substrate **145f** (entry 5, ***Table 4.2.3***). Besides that, we were also surprised to find a more pronounced difference in enantioselectivity between ligands (*R,R*)-**299a** (52% e.e., entry 13) and (*R,R*)-**299f** (97% e.e., entry 14) than between (*S,S*)-**296a** (75% e.e., entry 1) and (*S,S*)-**296f** (97% e.e., entry 7). Both (*S,S*)-**296f** and (*R,R*)-**299f** gave excellent enantioselectivity (97% e.e., entries 7 and 14). Basing on these results, we noticed an interesting trend that for substrate **145e**, ligands with electron-withdrawing aryl substituents gave better enantioselectivity than those with electron-donating groups, (e.g. comparing entry 2 with 3, entry 4 with 5 and 6, and entry 7 with 8). Interestingly, this scaffold could afford as high as 97% e.e. for this substrate when the aryl group of the ligand was 3,5-di(trifluoromethyl)phenyl group ((*S,S*)-**296f,** entry 7). These results show that the electronic affect plays a very important role in the enantioselectivity towards this linear substrate. An straightforward comparison between ligands fixed 1,4-substituent groups can be seen in ***Scheme 4.2.1***.




***Scheme 4.2.1*** Enantioselectivity comparision between ligands with fixed 1,4-substituent groups for 3-nonen-2-one. Functional groups which have an obvious electron-withdrawing effect are shown in green color while the electron-donating groups are in red.

It can also be seen that the enantioselectivities are also sensitive to the changes in groups at 1,4-positions from the results of entries 1, 9, 10 and 11, where all the ligands share the same Ph groups at 2,5-positions while the 1,4-positions are varied. Comparing enantioselectivity of the reaction of ligand (*S,S*)-**296a** and (*S,S*)-**274** with 2-cyclohexenone **145a** and 3-nonen-2-one **145e** (***Table 4.2.1***, entry 1 and 3; ***Table 4.2.2***, entry 1 and 10), in which the ligands have similar steric demands at the 1,4-positions but with different electronic properties, it could be found that for 2-cyclohexenone both (*S,S*)-**296a** and (*S,S*)-**274** gave very similar e.e. (89% for (*S,S*)-**296a** and 88% for (*S,S*)-**274**) but for for 3-nonen-2-one (*S,S*)-**296a** gave 75% while (*S,S*)-**274** gave 57%. Although the difference in enantioselectivity between (*S,S*)-**287a** and (*S,S*)-**291** for 3-nonen-2-one is not as significant as that between (*S,S*)-**296a** and (*S,S*)-**274**, similar phenomena can be observed from (*S,S*)-**287a** and (*S,S*)-**291** for the 2-cyclohexenone (97% e.e. by (*S,S*)-**287a**, 99% e.e. by (*S,S*)-**291**) and 3-nonen-2-one (67% e.e. by (*S,S*)-**287a**, 71% e.e. by (*S,S*)-**291**). These could be clarified in ***Scheme 4.2.2***.




***Scheme 4.2.2*** Enantioselectivity comparision between ligands with fixed 2,5-substituent groups for 2-cyclohexenone and 3-nonen-2-one. The steric demands of these four ligands are listed in a rough decreasing order from left to right. The 1,4-position groups which have an obvious electron-withdrawing effect was shown in green color.

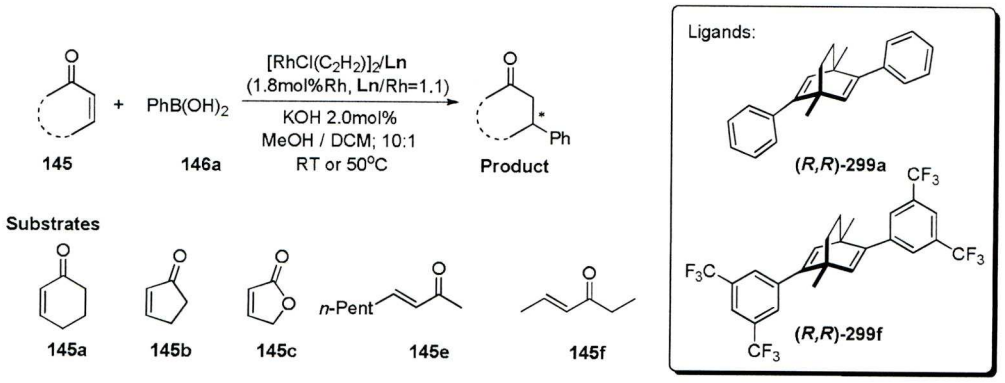
These results again suggested two things. Firstly, besides the obvious steric affect, it seems the electronic property of substituents at 1,4-positions also play important role in the enantioselectivity; second, for the linear substrate, the electronic effect seems to be the dominant factor that affect the enantio-selectivity.

As expected, (*R,R*)-**299h**, having two methyl groups at 1,4-positions (which are the most electron donating groups) and the most electron rich aryl 3,4,5-(trimethoxyl)phenyl at the 2,5-positions (entry 15, ***Table 4.2.2***), gave the lowest e.e. for this substrate of all ligands (49% e.e.). The electronic effect brought about by the two methyl groups is so strong that even the (*R,R*)-**299a** with phenyl group at 2,5-positon only gave 52% e.e. However, this detrimental electronic effect could be offset by introducing high electron withdrawing aryl groups at the 2,5-positions. For example, the 1,4-dimethyl-2,5-(3',5'-di(trifluoromethyl)phenyl) substituted ligand ((*R,R*)-**299f**, entry 14) could achieve excellent e.e. comparable to (*S,S*)-**296f** ( entry 7) despite the detrimental electronic effect given by the 1,4-dimethyl.

We also studied another [2.2.2] ligand system where the substituent groups at the 1,4-positions are hydrogen (entries 16-19). It was found that introducing a methyl ester group at the *para*-position of the phenyl at 2, 5-positions of the ligand does not change the e.e. a lot (92%, entry 17, (*R,R*)-**27c**) compared the phenyl derivative (94%, entry 16, (*R,R*)-**27a**). However, we also observed an obvious drop of the e.e. when the aryl at the 2,5-position was 3,4,5-(trimethoxyl)phenyl (83% e.e., entry 18, (*R,R*)-**27d**). There was no reaction when the aryl is 2-formylphenyl (entry 19, (*R,R*)-**27e**).

This relationship between electronic effect and enantioselectivity could be related to the chemical shift of the olefin proton observed in $^1$H NMR. The chemical shift of the proton relates to degree of electronic shielding to the proton, and the electron density of the π–electons. The higher of the chemical shift of the proton, the lower the electron density of the diene bond. It could be found that for closely related structures (diene ligands (*S,S*)-**296a-h**, entry 1 to 8) the results followed a trend: the higher chemical shift of olefin proton, the higher enantio-selectivity. Generally, this rule is quite accurate even between dienes having different 1,4-substitutent groups (comparing entry 9, 10 and 11).

***Table 4.2.3*** Comparison between **(*R,R*)-299a** and **(*R,R*)-299f** with varies substrates.




| Entry[a] | Enones | Products | Yield(%)[b] **(*R,R*)-299a** | [e.e. (%)][c] **(*R,R*)-299f** | Config. |
|---|---|---|---|---|---|
| 1 | **145a** | **147** | 98 [99] | 92 [98] | *R* |
| 2 | **145b** | **163** | 100 [99] | 80 [96] | *R* |
| 3 | **145c** | **164** | 95 [98] | 76 [92][d] | *R* |
| 4 | **145e** | **166** | 99 [52] | 99 [97] | *S* |
| 5 | **145f** | **300** | 99 [67] | 99 [95] | *S* |

[a] Reaction conditions: **145** (0.5mmol), **146a** (0.6mmol for **(*R,R*)-294a**, 1.0 mmol for **(*R,R*)-294f**), $[Rh(C_2H_4)_2Cl]_2$ (1.8 mol% Rh), Ligand **Ln** (2 mol%), $MeOH/CH_2Cl_2$; 10:1 (2.3ml), KOH (2 mol%) (2.3ml), 3h., room temperature, 1hr at 30°C for **(*R,R*)-294a** and 3hr for **(*R,R*)-294f.** [b] Yield of isolated product. [c] *Ee*'s were determined by chiral HPLC (Chiralcel OD-H column). [d] 3.0eq. of phenylboronic acid used.

The methyl ester groups were replaced by methyl groups and ligands **(*R,R*)-299a** and **(*R,R*)-299f** were evaluated for a range of acyclic and cyclic enones **145a-e** (***Table 4.2-3***). As espected, similar significant differences were found for linear substrate **145f** between (*R,R*)-**299a** (67% e.e.) and (*R,R*)-**299f** (95% e.e.) as previous described for substrate **145e** between (*R,R*)-**299a** (52% e.e.) and (*R,R*)-**299f** (97% e.e.). Nevertheless, ligand (*R,R*)-**299a** gave excellent yields and selectivity for cyclic enones **145a-c** affording (*R*)-configured products. Results for cyclohexanone **145a** are similar to those obtained by Haysahi with diene ligand (*R,R*)-**27a** (***Table 4.2.1***, entry 7) [40]. For the lactone **145c**, both yield and e.e. were improved (95%, 98% e.e.) compared with Carreira's carvone derived ligand (80%, 90% e.e.) [103] and Darses' ligand (56%, 90% e.e.) [102]. Unlike (*R,R*)-**299a**, ligand (*R,R*)-**299f** gives excellent e.e. for both acyclic and cyclic enones in the expected product configuration, which is consistent with the space differentiation model for chiral $C_2$-symmetric diene ligands

developed by Hayashi [40, 49, 59, 78-80, 101].

Despite the discrepancy between acyclic and cyclic enones for (*R,R*)-**299a** in terms of enantioselectivity, we were pleased to find that the reactions completed smoothly at room temperature in 1h. with only 1.2 eq. of phenyl boronic acid, compared with at least 2 eq. for current diene ligands. The requirement for use of excess arylboronic acid is thought to arise as a result of the competing rhodium-catalysed protodeboronation [90-95, 196, 197]. This significant and unexpected advantage can reasonably be attributed to the 1,4-dimethyl substitution in ligand (*R,R*)-**299a** as compared to Hayashi's ligand (*R,R*)-**27a** and other ligands. On the other hand, in order to obtain a high yield when using our ligand (*R,R*)-**299f**, more than 2 eq. of phenyl boronic acid was required. For example, the yield of **164** was only 76% although 3 eq. phenyl boronic acid was consumed when ligand (*R,R*)-**299f** was used (entry 3, ***Table 4.2.3***).

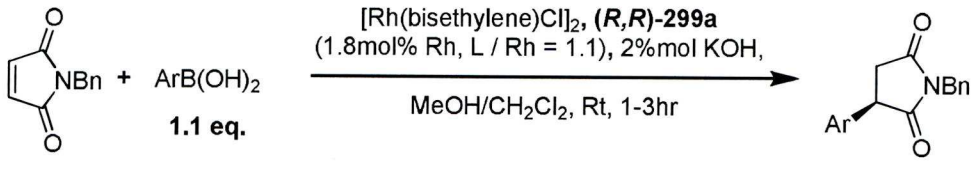
The only major difference between ligands (*R,R*)-**299a** and (*R,R*)-**299f** is that (*R,R*)-**299a** is more electron rich. These results suggest that the electronic properties of diene ligands are associated with activity, enantioselectivty (for linear substrates) as well as the productivity (ability to avoid the protodeboronation of aryl boronic acid). Increasing the electron density of the ligand benefits the reactivity and suppresses the protodeboronation reaction, but can undermine the enantioselectivity for linear substrates, as observed for (*R,R*)-**299a**. To maintain high enantioselectivity for the linear substrates requires the ligand to be less electron rich. However this can reduce some reactivity and allow the side reaction, as for (*R,R*)-**299f**.

### 4.2.2 Conjugate addition to *N*-benzyl maleiimide and 6-methyl coumarin

The asymmetric conjugate addition of aryl boronic acids to *N*-benzyl maleimide **301** is known to be a challenging reaction and the products are synthetically useful [198]. The chiral phosphine ligand, BINAP, gave only 70% yield and 58% e.e., while a chiral norbornadiene diene ligand gave 88% yield and 69% e.e. [107] The

phosphine-alkene hybrid ligands developed by Grützmacher and Hayashi both gave the desired product in high yield with Hayashi's hybrid ligand giving 89-95% e.e. [79, 80, 199]. However, multiple equivalents (3eq.) of arylboronic acid were required to ensure a high yield. Again it was found that ligand (*R,R*)-**299a** achieves both high activity and enantioselectivity for the formation of (*R*)-**174a-i** using only 1.1 eq. of $ArB(OH)_2$ (**146a-i**) at room temperature in 1 h (***Table 4.2.4***). This is the most efficient ligand for this transformation to date.

***Table 4.2.4*** Variation of Aryl boronic acid in asymmetric conjugate addition to *N*-benyl maleimide **301**




**301** **146a-i** **(*R*)-174a-i**

**146a**: Ar = Ph **146d**: Ar = 2-$FC_6H_4$ **146g**: Ar = 2-MeO-1-naphthyl
**146b**: Ar = 4-$MeC_6H_4$ **146e**: Ar = 3-$MeOC_6H_4$ **146h**: Ar = 4-$BrC_6H_4$
**146c**: Ar = 2-$CF_3C_6H_4$ **146f** : Ar = 4-$MeOC_6H_4$ **146i**: Ar = 4-$ClC_6H_4$

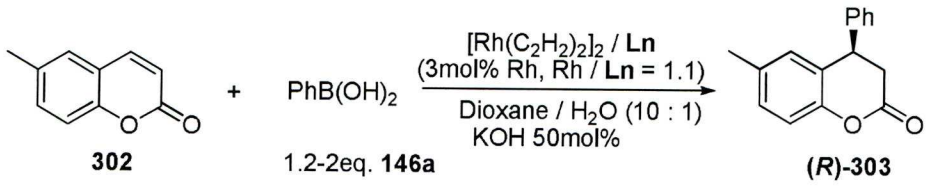
| Entry[a] | $ArB(OH)_2$ | Product[b] | Yield[c] | E.E. |
|---|---|---|---|---|
| 1 | **146a** | **174a** | 95 | 95 |
| 2 | **146b** | **174b** | 97 | 96 |
| 3 | **146c** | **174c** | 92 | 99 |
| 4 | **146d** | **174d** | 99 | 96 |
| 5 | **146e** | **174e** | 98 | 96 |
| 6 | **146f** | **174f** | 98 | 99 |
| 7 | **146g** | **174g** | 98 | >99 |
| 8 | **146h** | **174h** | 92 | 91 |
| 9 | **146i** | **174i** | 98 | 92 |

[a] Reaction conditions: **301** (0.5mmol), **146** (0.55mmol, $[Rh(C_2H_4)_2Cl]_2$ (1.8 mol% Rh), (*R,R*)-**299a** (2 mol%), MeOH/CH2Cl2; 10:1 (2.3ml), KOH (2 mol%) (2.3ml), stirring at room temperature for 3h. [b] Yield of isolated product. [c] Ee's were determined by chiral HPLC (chiralcel OD-H column).

The product resulting from the conjugate addition of phenyl boronic acid to 6-methylcoumarin **302** has been used in a synthesis of the urological drug tolterodine [199]. Examples reported by the Hayashi group show that phosphine ligands can give excellent e.e. (>99%), however 10 eq. of phenylboronic acid was necessary to achieve a high yield [199]. Only one example using a chiral diene for this reaction has been reported by Carreira, where 43% yield and 98% e.e. were obtained in the addition of

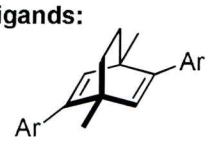
phenylboronic acid to the coumarin at 50°C using his carvone derived ligand [103]. We tested our ligands (*R,R*)-**299a**, (*R,R*)-**299e** and (*R,R*)-**299f** and also ran comparative reactions with Hayashi's ligand (*R,R*)-**27a** and Carreira's ligand (*R,R*)-**29** (***Table 4.2.5***).

***Table 4.2.5.*** Ligand screen for asymmetric conjugate addition to **302**



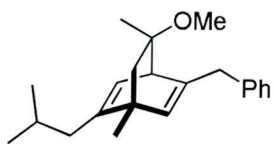

**302** 1.2-2eq. **146a** **(*R*)-303**

**Ligands:**




**(*R,R*)-299a:** Ar = Ph
**(*R,R*)-299e:** Ar = 4-$MeOC_6H_4$
**(*R,R*)-299f:** Ar = 3,5-$(CF_3)_2$-$C_6H_3$


**(*R,R*)-27a**




**(*R,R*)-29**

| Entry[a] | Ligand | temp.(°C) | Time(hr) | conv.[b](%) | Yield[c](%) | e.e. [d] (%) |
|---|---|---|---|---|---|---|
| 1 | **(*R,R*)-27a** | 30 | 24 | <5 | -- | n.d. |
| 2 | **(*R,R*)-27a** | 50 | 6 | 40 | 32 | 98 |
| 3 | **(*R,R*)-29** | 30 | 24 | 22 | 20 | 98 |
| 4 | **(*R,R*)-29** | 50 | 6 | 48 | 39 | 98 |
| 5 | **(*R,R*)-299a** | 30 | 24 | 66 | 63 | 98 |
| 6 | **(*R,R*)-299a** | 50 | 6 | 85 | 72 | 98 |
| 7 | **(*R,R*)-299f** | 50 | 24 | 0 | 0 | - |
| 8 | **(*R,R*)-299e**[e] | 30 | 3 | 100 | 95 | 98 |

[a] Reaction conditions: Ref [101]. [b] conversion was determined with GC, EC-1 column and calibrated with standard **302** and **303**. [c] isolated yield. [d] E.e.'s were determined by chiral HPLC (chiralcel OD-H column). [e] As [a] except 25mol% KOH and 1.2 eq. $PhB(OH)_2$ were used.

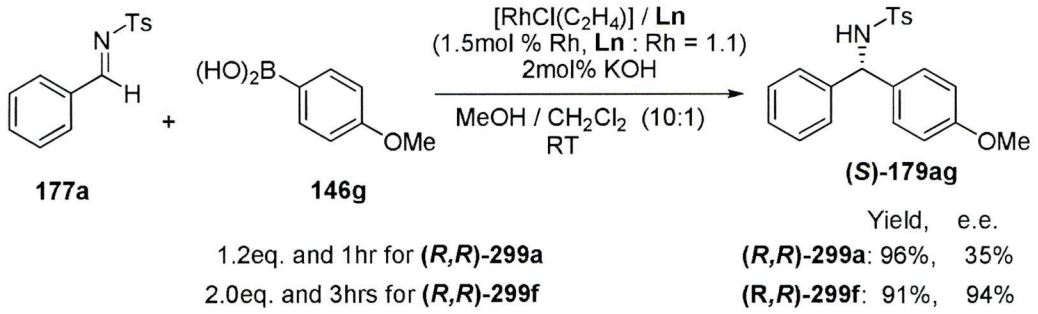
The enantioselectivity for all ligands was uniformly high (98% e.e.). However, a remarkable difference in reaction rate and yield was found between the ligands when comparing conversion and isolated yield at 30°C and 50°C after 6h. and 24h. Hayashi's ligand (*R,R*)-**27a** give the lowest rate of conversion, Carreira's ligand (*R,R*)-**29** gave increased conversion, our (*R,R*)-**299a** gave a further increase but the most active ligand for this reaction was ligand (*R,R*)-**299e**, containing the

4-methoxyphenyl groups. This gradual increase in reactivity may be attributed to an increase in electron density in the ligand system; Hayashi's diene (*R,R*)-**27a** contains no bridge substituents, Carreira's diene (*R,R*)-**29** contains one methyl substituent but the 2, 5-positions are alkyl-substituted rather than aryl, ligand (*R,R*)-**299a** has two bridge-head methyl groups and (*R,R*)-**299e** has two bridge-head methyl groups and electron donating 4-methoxyphenyl substituents. This is corroborated by the fact that our electron deficient ligand (*R,R*)-**299f** gave no reaction for this substrate.

From those experiments described above, again it is suggested that for the 1,4-disubstituted scaffold: 1) For the linear substrates, the enantioselectivity was greatly affected by both electronic and steric factors of 1,4-substituted groups and also the electronic effect from the 2,5-groups while the cyclic compound is mainly affected by sterific factors. 2) Electron rich ligands like (*R,R*)-**299a** gives relatively higher activity than the electon poor ones. Another advantage of electronic rich ligands is a much higher atom efficiency. Only 1.2 eq. of arylboronic acid are required to achieve high yield while the electronic poor ligands such as (*R,R*)-**299f** need 2-3 equivalents. This suggests that the electronic properties are also related to atom efficiency in the reaction. The electronic rich ligands can successfully surpress the side reaction of deboronation of aryl boronic acids, which is a significant problem existing in both phosphine and current diene ligand-catalyzed arylation reactions.

### 4.2.3 Addition to tosylimine

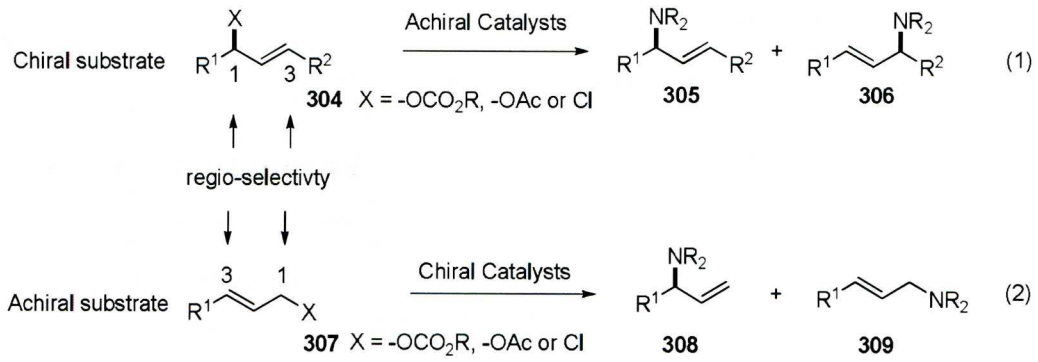
In order to further test this electronic effect, ligands (*R,R*)-**299a** and (*R,R*)-**299f** were examined for the 1,2-addition to tosyl imine **177a**, which can be categorized as a linear substrate (***Scheme 4.2.3***). The results were as expected; as with the 1,4-addition to linear enones, (*R,R*)-**299a** gave much higher reactivity but lower e.e. with less arylboronic acid, while (*R,R*)-**299f** gave excellent enantioselectivity but lower reactivity and some proto-deboronation side-reaction.



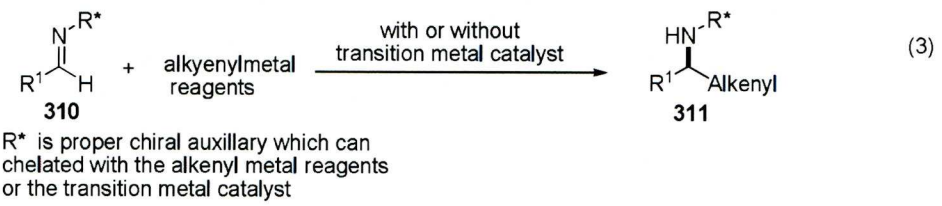

***Scheme 4.2.3*** Asymmetric arylation of *N*-tosyl benylimine

Although both α-branched allylic amine (like compound **305** and **306**) [200-203] and aryl aryl methyl amine (such as **179ag**) [116, 204-206] feature in complex molecules. the alkenyl addition products like **305** and **308** are more valuable from the synthetic view than the diarylmethylamine (*S*)-**179ag**. Chiral allylic amine can be converted into many useful chiral synthons by virtue of the olefin moiety [207-209]. However, methodologies for obtaining 1-aryl-2-propenylamines in non-racemic form are limited, as described in ***Scheme 4.2.4***. One apporach is metal-catalyzed substitution of allylic carbonates, acetates or halides, which can be carried out in two ways (equation 1 and 2, ***Scheme 4.2.4***). The first is to use chiral allylic substrates **304** and achiral catalyst (equation 1) [210-212], while the second alternatively employs achiral allylic substrates **307** and chiral catalysts (equation 2) [213-219]. Apart from the common problem of regioselectivity, both approaches share the same limitation in substrates diversity. The first method requires synthesis of the chiral allylic carbonate first and the later only affords vinyl-substituted amine (equations (1) and (2), ***Scheme 4.2.4***).

**1) Allylic Substitution**




**2) Chiral auxillary assisted diasteroselective addition**

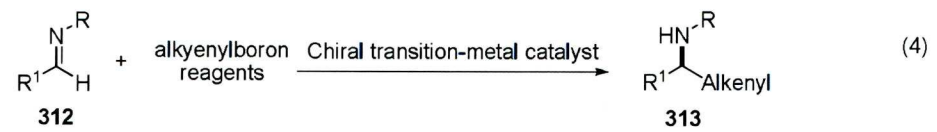



310

311

R* is proper chiral auxillary which can chelated with the alkenyl metal reagents or the transition metal catalyst

**3) Potential methodology for synthesis of chiral allylic imines**




312

313

***Scheme 4.2.4*** Ttransition metal involved methodologies for synthesis of chiral allylic amines

Another method to access this type of product is the addition of alkenylmetal reagents to imines containing chiral auxillary groups (equitation (3)) [220-233]. For example, Kibayashi and co-workers [226] reported the synthesis of enantiopure (*R*)-allylamines by the reaction of benzaldehyde oxime chiral ether with vinyl lithium and the subsequent cleavage using Zn – AcOH. Most recently the Ellman group developed a Rh(COD)Cl catalyzed addition of potassium alkenyltrifluoroborates to chiral *N*-(*tert*-butanesulfinyl)-aldimines to afford α-branched allylic amines with excellent diastereoselectivity [234]. Nevertheless, the necessity for stoichiometric amount of chiral auxiliary is a obvious disadvantage. An alternative method is to resolve the

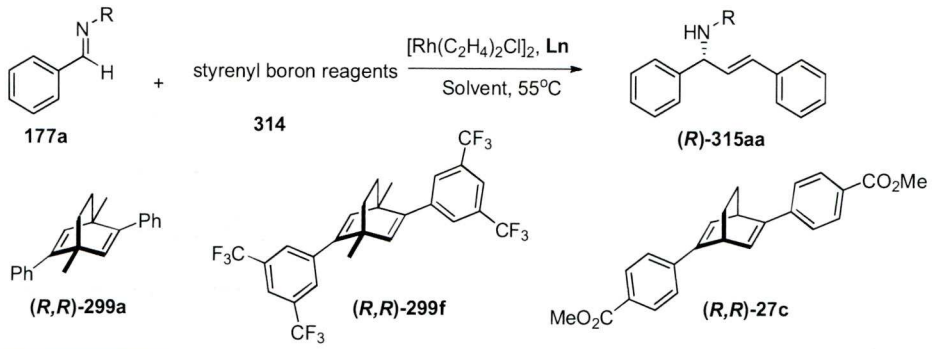
racemic allylic amine by classical resolution [235] or using enzyme [236], although stoichiometric usage of chiral acid or substrate specificity need to be addressed.

An ideal transformation for the synthesis of chiral α-branched allylic amines would be the addition of alkenyl boron reagents to the imines, catalyzed by a chiral catalyst (equation (4), ***Scheme 4.2.4***). The advantages of this method are: 1) avoidance of using stoichiometric amount of chiral reagents, which make it more economic and 2) due to the large varieties of readily accessible imines and alkenyl boron reagents, this methodology would allow access to a diverse range of products.

We started by investigating the alkenylation of tosylimine **177a** with styrenyl boron reagents **314**. We were very surprised to find that there was no reaction at all upon switching from aryl to alkenyl boron reagents using standard literature procedures with our most active ligand (*R,R*)-**299a** (entryl, 2, 8 and 10; ***Table 4.2.6***) [59, 69, 102, 234]. Changing the imine activating group from tosyl to diphenylphosphinoyl did not help (entry 2, 3 and 7).

An inspiring result was obtained by using potassium styrenyl trifluoroborate instead of styrenyl boronic acid with 1 eq. of triethylamine in methanol and dichloromethane. Both (*R,R*)-**299a** and (*R,R*)-**299f** gave some yield of **315**. Although the yield was not encouraging, we were please to find that the results were still consistent with the electronic property trend that governs the enantioselectivity and activity described previously (entry 5 and 6). We noticed that the low yield was caused by the decomposition of imine **177a**. However, increasing the amount of base was not helpful: the starting material remained while the potassium styrenyl trifluoro borate underwent complete hydrolysis and became styrenyl boronic acid.

***Table 4.2.6*** Chiral diene-Rh catalyzed alkenylation of imine




| entry | R | 314 | Ln | Solvent | additive | Yield | e.e. |
|---|---|---|---|---|---|---|---|
| 1 | tosyl | Ph–B(OH)2 | (*R,R*)-299a | MeOH / DCM (10:1) | 2% KOH | 0 | -- |
| 2 | tosyl | Ph–B(OH)2 | (*R,R*)-299a | Dioxane / $H_2O$ (4:1) | 50% KOH | 0 | -- |
| 3 | $Ph_2P(O)$- | Ph–B(OH)2 | (*R,R*)-299a | MeOH / DCM (10:1) | 2% KOH | 0 | -- |
| 4 | $Ph_2P(O)$- | Ph–B(OH)2 | (*R,R*)-299a | Dioxane / $H_2O$ (4:1) | 50% KOH | 0 | -- |
| 5 | tosyl | Ph–$BF_3K$ | (*R,R*)-299a | MeOH / DCM (10:1) | 1 eq. $Et_3N$ | 30% | 31% |
| 6 | tosyl | Ph–$BF_3K$ | (*R,R*)-299f | MeOH / DCM (10:1) | 1 eq. $Et_3N$ | 10% | 65% |
| 7 | $Ph_2P(O)$- | Ph–$BF_3K$ | (*R,R*)-299a | MeOH / DCM (10:1) | 1 eq. $Et_3N$ | 0 | -- |
| 8 | tosyl | Ph–$BF_3K$ | (*R,R*)-299a | DMF / $H_2O$ (10:1) | 1 eq. $Et_3N$ | 0 | -- |
| 9 | tosyl | Ph–$BF_3K$ | (*R,R*)-299a | DMF / $H_2O$ (10:1) | 2.5 eq. $Et_3N$ | 0 | -- |
| 10 | tosyl | Ph–B(OH)2 | (*R,R*)-299a | toluene | 1.0 eq. $Et_3N$ | 0 | -- |
| 11 | tosyl | Ph–B(OH)2 | (*R,R*)-299a | toluene | 1.0 eq. $Et_3B$ | 60% | 52% |
| **12** | **tosyl** | **Ph–$BF_3K$** | (*R,R*)-27c | **toluene** | 1.0 eq. $Et_3B$ | **81%** | **99%** |
| 13 | tosyl | Ph–$BF_3K$ | (*R,R*)-27c | toluene | none | 20% | 95% |

[a] Reaction conditions: **177a** (0.3mmol), **314** (0.6 mmol), [{Rh($CH_2$=$CH_2$)$_2$Cl}$_2$] (3mol% Rh), Ligand **Ln** (1.65 mol%), solvent (1ml) at 50°C, 6hr. [b] Yield of isolated product. [c] E.e.'s were determined by chiral HPLC on a Chiralcel OD-H column (see experiment sections, Chapter 5).

Based on the results described above, we assumed that the base may not be necessary, and on the contrary, a Lewis acid might accelerate this reaction. Consequently, if the reaction required some acid to activate it, protic solvents should be excluded due to the instability of **177a** in acidic conditions. We were very happy to find that the idea worked. In the presence of triethyl borane, (*R,R*)-**299a** gave moderate yield of **315**, even using styrene boronic acid (60% yield, entry 11). Moreover, the enantioselectivity also improved significantly compared with entry 5. Excellent result

was obtained with (*R,R*)-**27c**: 81% yield and 99% e.e. (entry 12). In addition, the triethyl borane was found to be essential to the reaction: without it the yield was only 20% with a slight drop e.e. (entry 13).

It is notable that this is the first example of Rh-diene-catalyzed highly enantioselective asymmetric alkenylation of an imines to produce an α-branched allylic amine.

### 4.2.4 Addition to aldehyde

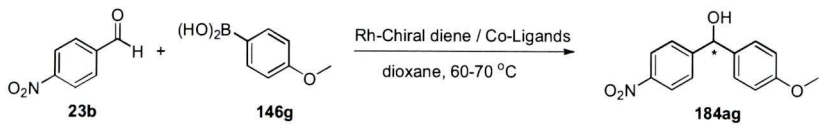
Direct alkylation of aldehydes has been a very useful methodology to afford chiral secondary alcohol in organic synthesis. The most frequently used alkyaltion reagents are organo lithium [237], magnesium [237] and zinc [238] reagents. However, there are only a few examples where the organoboron reagents have been used [122-126]. Miyaura was the first to report the Rh-catalyzed 1,2-addition to aromatic adehydes with aryl or alkenyl boronic acids in an achiral manner [239]. Fürstner's work proved that *N*-heterocyclic carbenes were suitable ligands for this transformation and the substrate scope was expanded to aliphatic aldehydes with good yields [240].

The asymmetric variant was attempted with a series of chiral bis-oxazoline ligands by Frost and co-workers [122]. However the highest e.e. was only 9%. In 2006, Zhou and co-workers reported Rh-catalyzed arylation of aromatic aldehydes in excellent yield (88-97%) with moderate to good e.e. (62-87%) by using a chiral monodentate phosphite based on 1,1'-spiro-biindane-7,7'-diol as ligand [127]. Recently Miyaura and co-workers developed a chiral phosphoramidite ligand-Ru catalyst, which could catalyze arylation of aromatic aldehydes to afford diaryl methanol in both excellent yield and enantioselectivity (average yield of ca. 87% and e.e. of ca. 90%) [128].

The only example of chiral diene-Rh catalyzed addition of arylboronic acids to aldehydes was reported by Hayashi and co-workers, in which diene **42e** (page 20, ***Scheme 1.2.12***, Chapter 1) was used and chiral diarylmethylalcohol was obtained in high yield and e.e. [67] ( averge yield of >90% and e.e. of 85%).

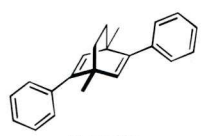
We also carried out this reaction with our chiral diene ligands for the addition of *p*-methoxyphenyl boronic acid **146g** to *p*-nitrobenzaldehyde **23b** and the results are shown in ***Table 4.2.7***.

***Table 4.2.7*** Combinatorial screen of chiral diene & co-ligands catalyzed asymmetric arylation of aldehyde

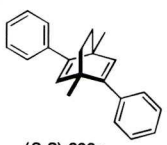



**23b** **146g** **184ag**

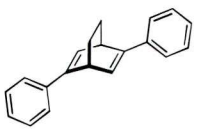
**Chiral diene ligands**



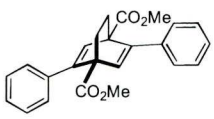
(*R,R*)-299a



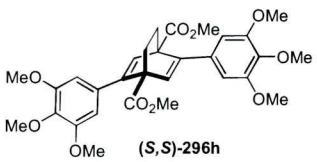
(*S,S*)-299a



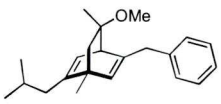
(*R,R*)-27a



(*S,S*)-296a

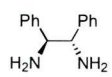


(*S,S*)-296h

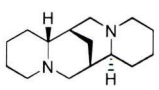


(*1R,4R,8S*)-29b

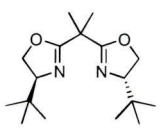
**Co-ligands**



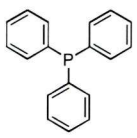
**316** (*S,S*)-DPEN



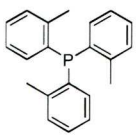
**317** Sparteine



**318** *t*-Bu-BOX



**319**



**320** (*o*-tolyl)$_3$P

| Entry[a] | Ln | Co-ligand | t (hr) | Yield[b] | e.e. of **184ag**[c] |
|---|---|---|---|---|---|
| 1 | **(*R,R*)-299a** | None | 12 | 98 | 31 |
| 2 | **(*R,R*)-299a** | (*S,S*)-DPEN | 12 | 65 | 28 |
| 3 | **(*R,R*)-299a** | Sparteine | 24 | 50 | 28 |
| 4 | **(*R,R*)-299a** | $Ph_3P$ | 24 | 80 | 35 |
| 5 | **(*R,R*)-299a** | (*S,S*)-*t*-Bu-BOX | 6 | 98 | 35 |
| 6 | **(*S,S*)-299a** | (*S,S*)-*t*-Bu-BOX | 6 | 96 | -35 |
| 7 | **(*R,R*)-27a** | None | 12 | 80 | -31 |
| 8 | **(*S,S*)-296h** | None | 12 | 82 | 5 |
| 9 | **(*S,S*)-296a** | (*o*-tolyl)$_3$P | 24 | 68 | 15 |
| 10 | **(*1R,2R,8S*)-29** | None | 12 | 95 | -9 |

[a] Reaction conditions: **23b** (0.5mmol), **146g** (0.6mmol, [Rh(C2H4)2Cl]2 (1.8 mol% Rh), chiral diene ligand (2 mol%), co-ligand (2 mol% if used), NaOMe (2 mol%), Dioxane (1ml), stirring at 70°C for 6-24hrs. [b] Yield of isolated product. [c] Ee's were determined by chiral HPLC (Chiralcel OB-H column).

Firstly the active ligand (*R,R*)-**299a** was used and the reaction cleanly afforded

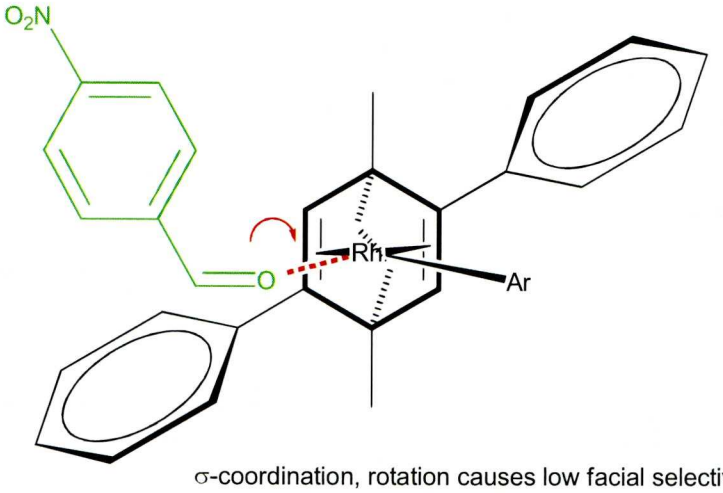
(*p*-nitrophenyl)(*p*-methoxyphenyl)methanol in excellent yield but the e.e. was quite low (98% yield, 33% e.e., entry 1). In order to increase the enantioselectivity, chiral co-ligands were added. However, it was found that neither (*S,S*)-DPEN nor sparteine gave any promotion to the enantio-selectivity, and on the contrary, both of them retarded the reactions (entry 2 and 3), the achiral ligand like triphenylphosphine also did not increase the enantioselectivity (entry 4).

The chiral BOX co-ligand greatly promoted the reactivity but did not affect the enantioelectivity at all. Combination of (*S,S*)-*t*-Bu-BOX with (*R,R*)-**299a** and (*S,S*)-**299a** gave the antipodal product with same enantioselectivity, which indicates that the chirallity of BOX co-ligand exerted no effect or the outcome. On the other hand, despite the diasteroisomeric difference in the catalysts, both provided higher reactivity compared to the pure diene system or diene combined with other co-ligands systems (entries 5 and 6).

Interestingly, diene (*R,R*)-**27a** (entry 7), which has the same configuration as (*R,R*)-**299a**, gave the product of opposite configuration compared with (*R,R*)-**299a** (entery 1). The only difference between (*R,R*)-**27a** and (*R,R*)-**299a** is the 1,4-substituents, the former is hydrogen while the later is methyl. Moreover, the ligand with 1,4-methoxycarbonyl groups and 2,5-(3',4',5'-trimethoxyphenyl) groups gave the lowest e.e. (entry 8). Combination of ligand (*R,R*)-**296a** and tri(*o*-tolyl)phosphine also only gave 15% e.e. (entry 9). Carriera's diene only gave 9% e.e. (entry 10).

With the aid of the chiral recognition model in ***Scheme 4.2.5***, we can suggest an explanation for the low enantioselectivity here. In this view, the aldehyde coordinates to the Rh with the lone pair electrons on the oxygen atom instead of electrons in the $\pi$ orbital of C=O bond. As a result, this $\sigma$-type coordination will lead to the low facial selectivity due to the free rotation of the bond. In addition, a higher temperature (60-70°C) is required to accomplish the addition of the aryl-Rh moiety to the C=O

bond compared to the enones. All these factors could reduce the enantioselectivity.



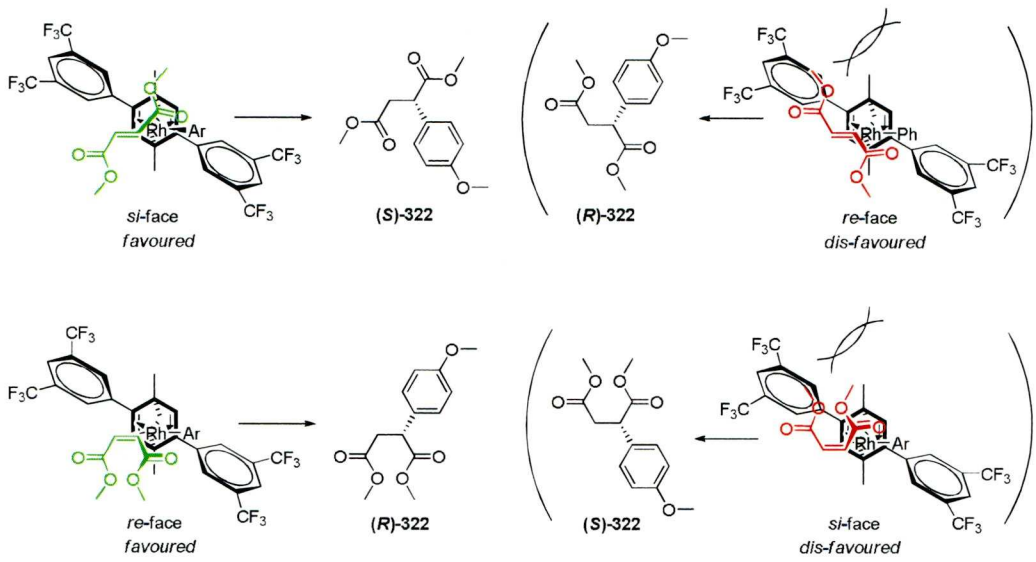

***Scheme 4.2.5*** Assumed chiral recognition model of arylation of aldehyde

### 4.2.5 Influence of the geometry of the enone's C=C bond

The phenomenon that ligand (*R,R*)-**299a** and (*R,R*)-**299f** exhibit contrasting enantioselectivity for the linear substrates aroused our interest. The bridge-head substitutuents in the ligand were not detrimental for cyclohexenone **145a** (or other cyclic enone substreate as proved earlier), and according Hayashi's space differentiation model [40, 49, 59, 78-80, 101], it is reasonable to assume that it was not simply caused by the substrate shape selectivity. We assume that the low enantioselectivity using (*R,R*)-**299a** is attributable to isomerizition of enone's C=C bond at some point during the reaction.

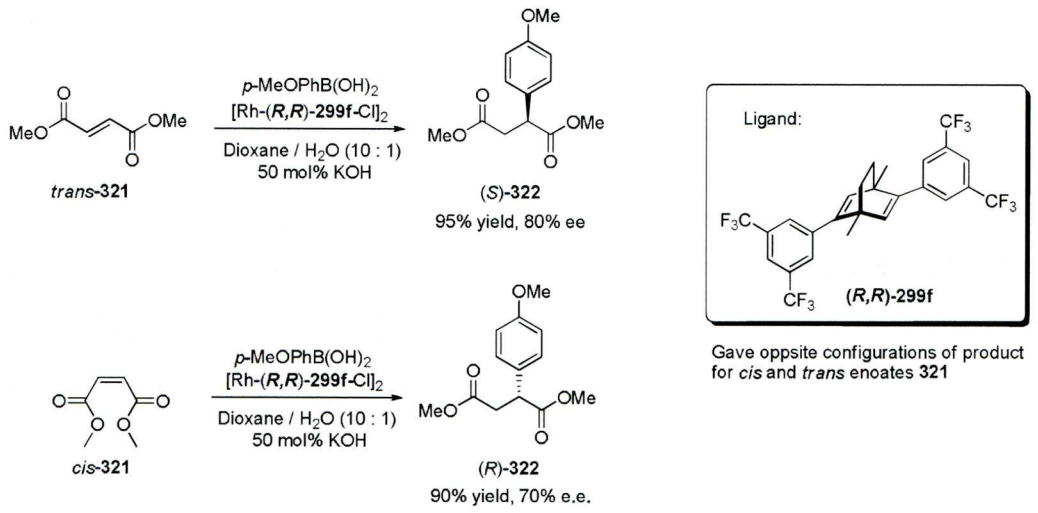
We designed a set of experiments to test this assumption further. According to the chiral recognition model shown in (page 39, ***Fig 1.4.1***, Chapter 1), it is clear that the geometry of the C=C bond should be important in determinating the configuration of the product. For instance, the use of the (*R,R*)-**299f** diene ligand with 2-cyclohexenone would give the *R* product, so it is reasonable to assume that the (*R,R*)-**299f** diene ligand would give the same selectivity with *cis*-3-hexen-2-one, which share the same C=C bond configuration and a similar structure to 2-cyclohexenone (except it is an acyclic enone).

Based on this assumption we conducted the following investigation. A pair of geometric isomers of Michael accepters were chosen to be tested with ligands with different electronic properties. Here the dimethyl maleate and dimethyl fumarate were selected as substrates due to their commercial availability. Firstly, this pair of geometric isomers was subjected to the reaction catalyzed by (*R,R*)-**299f**, and analysis of the configuration of products was made by using the model in ***Scheme 4.2.6***.



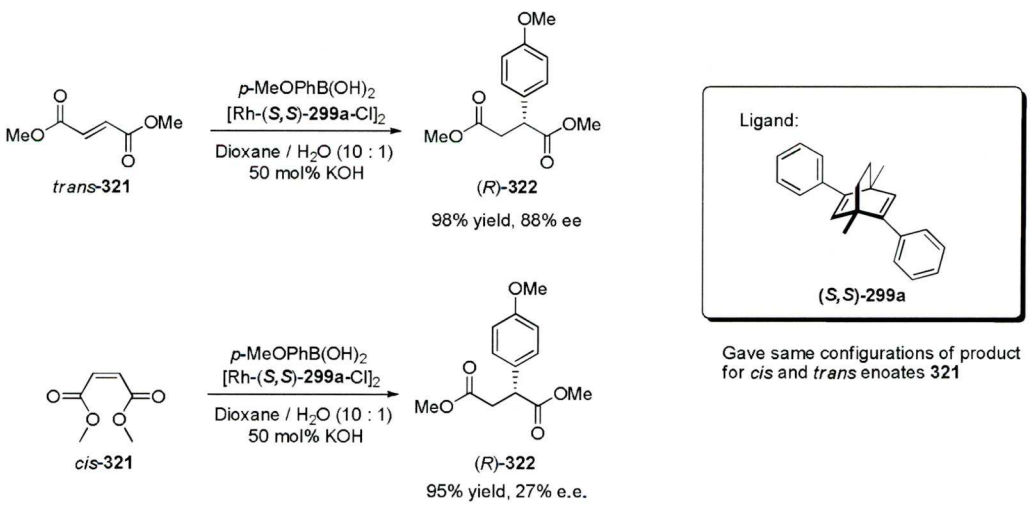

***Scheme 4.2.6*** Chiral recognition model of chiral diene ligands

The results of the analysis are shown in ***Scheme 4.2.6***. For the *trans*-enoate, dimethyl fumarate, the (*R,R*)-**294f** would give *S*-addition product, but for the *cis*-enoate dimethyl maleate, the *R*-product is favoured. The actual experiment results were entirely consistent with the theoretical analysis: the *trans*-**321** gave (*S*)-**322** (95% yield, 80% e.e.), and *cis*-**321** gave (*R*)-**322** with moderate e.e (90% yield, 70% e.e.) but sufficient enough to support it (***Scheme 4.2.7***).



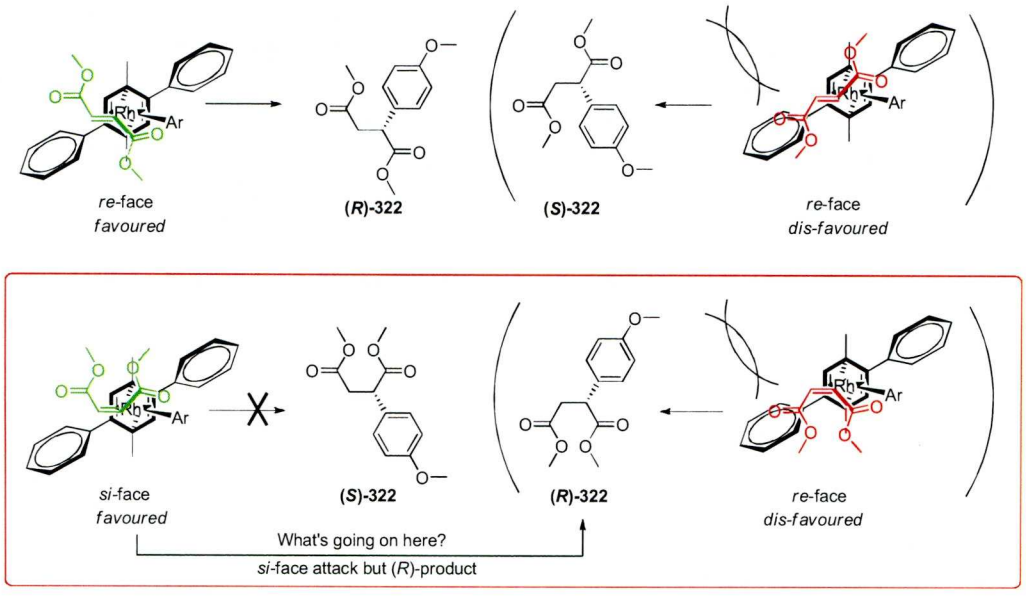

***Scheme 4.2.7*** Chiral diene-catalyzed conjugate addition to geometric isomer of enoates *cis* and *trans* **321**

The same reactions were carried out with a different ligand (*S,S*)-**299a** (***Scheme 4.2.8***). Here, according to the model, the *trans*-**321** should give (*R*)-**322** and the *cis*-**321** give (*S*)-**322**. However, the experimental results were not consistent with the theoretical analysis: the *trans*-**321** was converted into (*R*)-**322** with good e.e. (88%), which was in agreement with the recognition model; but the *cis*-**321** did not afford (*S*)-**322**, instead (*R*)-**322** was obtained with a low e.e. (27%, ***Scheme 4.2.8***).




***Scheme 4.2.8*** Chiral diene-catalyzed conjugate addition to geometric isomer of enoates *cis* and *trans* **321**

If we go back to analyze the space differentiation model again (***Scheme 4.2.9***), we can find this discrepancy happens with the *trans*-enoate **321**, which was supposed to yield (*S*)-**322** with ligand (*S,S*)-**299a** but (*R*)-**322** with a low e.e. was obtained instead. Considering the low e.e. for (*R,R*)-**299a** with *trans*-3-nonen-2-one (**145e**) and *trans*-4-hexen-3-one (**145f**) (entries 4 and 5, ***Table 4.2.3***), one thing for sure is that something happens before the enone insertion to Rh-Aryl species.




***Scheme 4.2.9*** Chiral recognition model of chiral diene ligands

A reasonable assumption for this phenomenon is that the acyclic enone or enoate underwent different degrees of isomerization when they were exposed to the electron rich chiral diene-Rh complex. To be more precise, the isomerization may happen more quickly with the electron rich chiral diene-Rh-Ary species. In the addition for *cis*-**321** shown in ***Scheme 4.2.8***, we did not observe any isomerized *trans*-**321** during the course of the reaction. Running this reaction under the same conditions but without addition of *p*-methoxybenzeneboronic acid for 48 hrs, less than 10% of the isomerized *trans*-**321** was found, however, this amount is not large enough to account fot the result observed because theoretically over 50% *trans*-isomer is necessary to

turn round the out come of the product's absolute configuration. So another possible assumption for this phenomenon is that there is quick equilibrium in the isomerization between the *cis* and *trans* isomer.

Similar issues occurred in the Cu-catalyzed asymmetric conjugate additions. Imamoto and Mukaiyama observed that the absolute stereochemistry of products was only related to the ligand and not affected by the geometry of the enone [241]: by using copper bromide and (*S*)-1-methyl-2-hydroxymethylpyrrolidine as catalyst and methylmagnesiumbromide as addition reagent, both (*Z*)- and (*E*)-1,3-diphenyl-2-propen-1-one gave (*S*)-1,3-diphenyl-3-methyl-propan-1-one with almost the same e.e. A similar phenomenon was also found for phosphine ligands [242]. However, a Tol-BINAP and CuI complex was found to be not only a highly enantioselective catalyst but also able to differentiate the geometry of C=C bond in the conjugate addition to enoate substrates [243]. In most cases, generally the *E* type accepter would afford high e.e. but the *Z* type gave the same configuration product with low e.e. [244].

In principle, in the Cu-catalyzed asymmetric conjugate addition, the geometry of the C=C bond affects the absolute stereochemistry in a similar way as described for the chiral diene ligands. The reason that absolute configuration is some times independent of the C=C bond geometry is due to the isomerization, which has been experimentally observed. However, despite intensive investigation on the Cu-catalyzed ACA reactions in the past several decades, the mechanism for the isomerization remains unsettled yet [244-249].

### 4.3 Summary

In summary, we have developed an efficient synthesis of the chiral $C_2$-symmetric bicyclic [2.2.2] diene ligand system that enables flexible substitution at the 1- and 4-positions. The synthesis is short, high yielding and includes a practical lipase resolution as a key step that can be done on a large scale and provides an attractive

alternative to resolution by chiral preparative HPLC. We have accessed a new series of 1,4-dimethyl 2,5- diaryl bicyclo [2.2.2] octadiene ligands for rhodium-catalysed asymmetric conjugate addition to a range of cyclic and acyclic enones. The addition of 1,4-methyl substituent groups in the ligands enabled us for the first time to observe a significant electronic effect which affects catalytic performance. The catalysts with electron rich ligands gave excellent activity for all substrates and excellent enantioselectivity for cyclic enones with high atom efficiency (only 1.1 - 1.2 equiv arylboronic acid), even for a challenging substrate such as 6-methylcoumarin. However, this advantage was not shared by linear enones as far as enantioselectivity is concerned. This problem could be abrogated by introducing electron-withdrawing groups on the ligand to achieve high ee for all types of substrate, although 2-3 equivalents of arylboronic acid are required to compensate for protodeboronation and to achieve high yield. To the best of our knowledge, this is the first time that such a unique electronic effect has been observed in diene ligands closely linking reactivity, enantioselectivity and productivity. Mechanistic studies to gain a deeper understanding into this phenomenon are ongoing.

This new group of chiral ligands was also investigated for the arylation of imines and aldehydes. It was found that for the imine addition reaction, the observation that the electronic properties of diene ligands relate to their catalytic performance is still consistent with the results obtained in conjugate addition to α,β-unsaturated carbonyl compounds.

Rh-diene catalyzed alkenylation to tosylimine was studied. Firstly a Lewis acid promoted, chiral diene-Rh catalyzed, highly enantioselective addition of the styreneyl group to tosylimine was established (81% yield, 99% e.e.). This method provides an alternative method to access a category of very important building block: α–branched allylic amines.

Preliminary results for the arylation of aldehydes suggest that the chiral diene – Rh

catalysts were not active enough for aldehydes compared with enones and tosylimines. Both the flexible σ–coordination and requirement of higher temperature may be responsible for the low e.e. The oxazoline co-ligand can promote the activity significantly, but surprisingly it does not affect the enantioselectivity at all. For this reaction, new ligands are needed.

Results from the diene-Rh-catalyzed conjugate additions to geometric isomers of enoates suggest that for the electron poor ligand (*R,R*)-**299f**, the absolute configuration of the product is dependent on the geometry of C=C bond. The *cis* and *trans* isomers gave products with opposite configurations, consistent with the space differentiation model for chiral diene ligands. However, the electron rich ligand (*S,S*)-**299a** gave a low e.e. for the *cis* enoate substrate **321** with the same configuration as obtained from the *trans* enoate. The relatively higher e.e. obtained with the electron rich ligand (*S,S*)-**299a** for the *trans* enoate **321** compared with the *trans* enone 3-nonen-2-one or *trans* 4-hexen-3-one may be attributable to the higher stability of the enoate under the reaction conditions. Our preliminary results suggest that the low e.e.'s obtained with the electron rich ligand **299a** with acyclic substrates may be caused by isomerization of the substrate C=C bond. Further investigation of the mechanism is ongoing.

# Chapter 5 Experimental Section

# Chapter 5 Experimental section

## 1 General

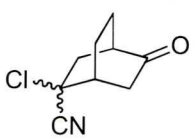
All solvents and reagents were used without further purification if not specified in the procedures.

NMR spectra were recorded on a Bruker AMX- 400 MHz spectrometer. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for $^1H$ NMR (400MHz) and chloroform-*d* (δ 77.05) for $^{13}C$ NMR (100MHz). Conversion was determined by GC on a Shimadzo GC with an EC-1 column, and the data was calibrated with standard samples. Enantiomeric excess was measured by normal phase HPLC on a Waters 2695 separation module equipped with a Waters 996 photo diode array detector. Separations were carried out using Chiracel AD, AD-H, AS-H and OD-H chiral column provided by Diacel company (columns and conditions under each compound later). The optical rotation data were recorded on a Perkin Elmer Polarimeter 343 Plus. The unit of it is deg $dm^{-1}cm^3\ g^{-1}$ and omited for simplification.

## 5.2 Experimental procedures and compound data

### 5.2.1 Compounds for the chemo-enzymatic synthesis chiral bicyclo[2.2.2]octan-2,5-dione

**5-chloro-5-cyano-bicyclo[2.2.2]octan-2-one (239)**

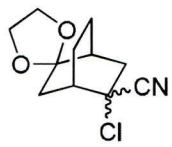



To a 250ml flask, 2-chloroacrylonitrile **238** (7.71 g, 45 mmol), 2-(trimethylsilyloxy)-1,3-cyclohexadiene) **219** (12.0 g, 137 mmol, 3eq.), hydroquinone (1.5 g, 13 mmol) and toluene (100 mL) were added. The mixture was stirred for 12 hr at 110°C. The black reaction mixture was filtered on a silica pad and

rinsed with hexane:EtOAc (4:1) to give a white solid (5.2 g, 63%). Several batches of this reaction were run, the best yield was 70% (1.6 g scale) and the lowest was 58% (15 g scale).

$^1$H NMR δ 2.68-2.72 (m, 1H), 2.64-2.67 (m, 1H), 2.49 (pent, $J$ = 2.8Hz, 1H), 2.31 (dt, $J$ = 15.8Hz, $J$ = 1.4Hz, 1H), 2.23 (app. pent, $J$ = 2.8Hz, 1H), 2.14 (dd, $J$ = 19Hz, $J$ = 3Hz, 1H), 2.00-2.11 (m, 1H), 1.64-1.75 (m, 3H), $^{13}$C NMR δ 210.8, 120.2, 55.9, 42.9, 42.4, 40.9, 39.6, 22.8, 21.1; Elemental analysis: $C_9H_{10}ClNO$, Calc.: C 58.86, H 5.49, N 7.63, Found: C58.98, H 5.51, N 7.59; HRMS CI+: {$[M+NH_4]^+$} Calc. 201.0795, Found 201.0797.

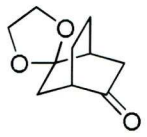
**5-Chloro-5-cyanobicyclo[2.2.2]octan-2-{2'-[1,3-dioxolane]} (240)**




Ketone **239** (3.2 g,170 mmol), ethylene glycol (5.3 g, 850 mmol, 5.eq.), TsOH (160 mg) and benzene (120 mL) were added to a 250 mL flask which was fitted a Dean-Stark apparatus. The mixture was heated to reflux for 12 hr then the reaction mixture was transferred to a separating funnel and EtOAc (100 mL) was added. The resulting solution was washed with 1N NaOH, water and brine in turn and then dried over anhydrous $MgSO_4$. Filtration and removal of solvent *in vacuo* gave the crude product, which was purified by flash column chromatography (Hexane : EtOAc 4 : 1) to give the ketal **240** as a colorless oil (3.9 g, 99%).

$^1$H NMR δ 3.80-4.10 (m, 4H), 2.5 9 (dd, $J$ = 15.2Hz, $J$ = 3.6Hz, 1H), 2.52 (dt, $J$ = 15.2Hz, $J$ = 2.5Hz, 1H), 2.41 (dt, $J$ = 15.2Hz, $J$ = 2.5Hz, 1H), 2.32 (app. pent, $J$ = 3.0Hz, 1H), 2.00-2.11 (m, 1H), 1.72-1.96 (m, 4H), 1.47-1.58 (m, 1H); $^{13}$C NMR δ 121.1, 108.5, 64.8, 64.5, 56.8, 41.4, 39.6, 36.0, 33.9, 22.5, 19.0; Elemental analysis: $C_{11}H_{14}ClNO_2$, Calc. C 58.03, H 6.20, N 6.15, Found: C58.28, H 6.22, N 6.11; HRMS CI+: $C_9H_{14}ClN_2O$, {$[M+NH_4]^+$} Calc. 245.1057, Found 245.1057.

**5-{2'-[1,3-dioxolane]}-bicyclo[2.2.2]octan-2-one (241)**

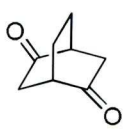


This compound was prepared according to reference [164].

The ketal **240** (3.0 g, 13mmol) was dissolved in DMSO (50 mL) in a 100ml flask, and to this mixture aqueous KOH (1.05 mL, 25M, 26 mmol) was added. This mixture was stirred at room temperature for 12hr. The reaction mixture was extracted with ether (100 mL) and then washed with water and brine separately. The organic solution was dried over anhydrous magnesium sulfate. Filtration and removal of solvent *in vacuo* gave the crude product which was purified with a flash silica column (Hexane : EtOAc 4 : 1) to give ketal-ketone **241** as a colorless oil (2.0 g, 85%).

$^1$H NMR δ 3.86-4.04 (m, 4H), 2.57 (dt, $J$ = 19.4Hz, $J$ = 3.0Hz, 1H), 2.40 (app. pent, $J$ = 3.0Hz, 1H), 2.13-2.19 (m, 2H), 2.08-2.11 (m, 2H), 2.02-2.08 (m, 1H), 1.73-1.90 (m, 2H), 1.51-1.61 (m, 1H); $^{13}$C NMR δ 215.9, 109.6, 64.8, 64.5, 44.7, 40.8, 39.1, 36.7, 22.4, 20.8; Elemental analysis: $C_{10}H_{14}O_3$, Calc. C65.91, H 7.74, Found: C65.78, H 7.76; HRMS CI+: $C_{10}H_{18}NO_3$, {$[M+NH_4]^+$} Calc. 200.1287, Found 200.1281.

**Bicylco[2.2.2]octan-2,5-dione (76)**

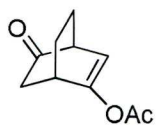


Ketal-ketone **236** (1.2 g, 6.5mmol) was dissolved in THF (20 mL) and 10% HCl aq. solution (3 mL) was added. The resulting mixture was stirred at room temperature overnight then extracted with dichloromethane (100 mL) followed by washing with water and brine. The organic solution was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* gave the pure diketone **76** as a white solid (if necessary the product was washed with water several times to remove the ethylene glycol residue) (900 mg, 99%).

$^1$H NMR δ 2.75 (pent, $J$ = 2.9Hz, 2H), 2.55 (dt, $J$ = 19.3Hz, $J$ = 2.3Hz, 2H), 2.49 (dd, $J$ = 19.3Hz, $J$ = 2.9Hz, 2H), 1.90-2.12 (m, 4H); $^{13}$C NMR δ 211.9, 45.5, 40.9, 22.7;

Elemental analysis: $C_8H_{10}O_2$, Calc. C69.54, H 7.30, Found: C69.80, H 7.32; LRMS CI+: $[M]^+$ 138.

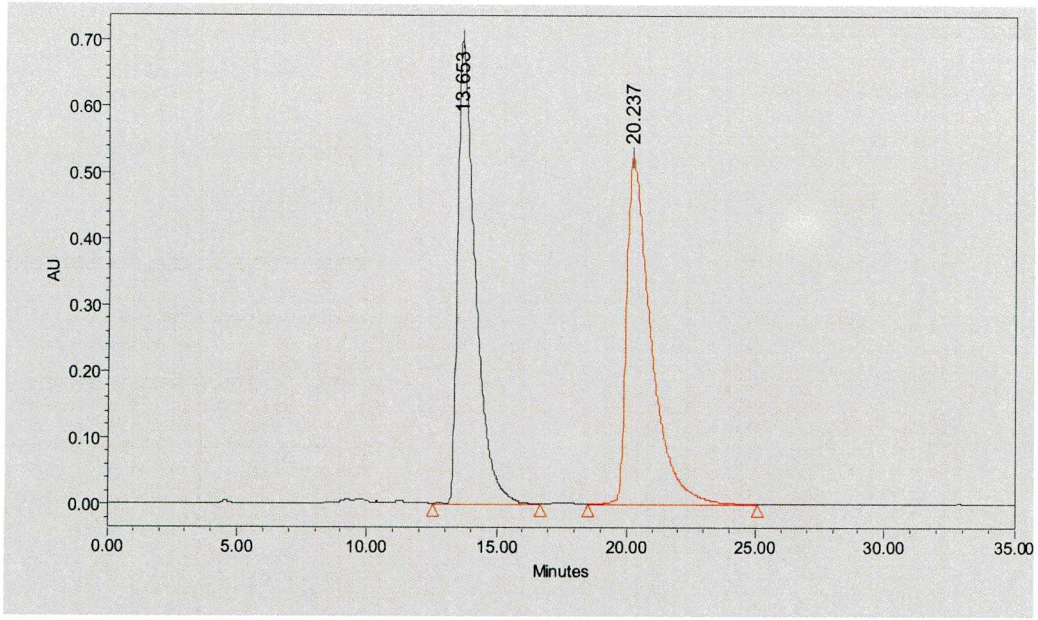
**(±)-2-Acetoxy-bicyclo[2.2.2]octan-2-en-5-one (247)**




Diketone **76** (1.38g, 10 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78$^0$C. To this solution LHMDS in THF solution (10.5 mL, 1.06M, 11 mmol) was added dropwise with stirring. The resulting mixture was stirred at -78$^0$C for an hour followed by addition of acetic anhydride (1.03 mL,1.12 g, 11 mmol). The resultant mixture was stirred at -78°C for 30min. then warmed to room temperature. Saturated $NaHCO_3$ aq. (200 mL) was added to quench the reaction before extraction with $Et_2O$ (3 × 50 mL). The ether layers were combined and dried over anhydrous $Na_2SO_4$. Filtration and removal of the solvent by rotary evaporation gave 1.8 g of crude product. The crude product was pure enough to be directly used in the enzyme resolution. Flash chromatography using hexane-EtOAc 4:1 as eluent gave pure product **(±)-247** as colorless oil (1.7g g, 95% yield).

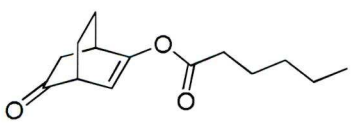
$^1$H NMR δ: 5.72 (dd, $J$ = 7.2, 2.7Hz, 1H), 3.15 (dt, $J$ =7.2, $J$ = 2.7Hz, 1H), 2.88 (q, $J$ = 2.7Hz, 1H), 2.41 (dt, $J$ = 18.2Hz, $J$ = 3.0Hz, 1H), 2.17 (s, 3H), 2.03 (dd, $J$ = 18.2, $J$ = 2.0Hz), 1.81-1.94 (m, 2H), 1.66-1.78 (m, 2H); $^{13}$C NMR δ: 211.8, 169.4, 156.6, 110.5, 47.9, 40.4, 36.9, 24.9, 23.6, 21.1; HRMS CI+: $C_{10}H_{16}NO_3^+$, $\{[M+NH_4]^+\}$ Calc. 198.1130, Found 198.1130.

HPLC condition: Chiracel AD column, Hexane:Isopropanol=95:5, 1ml / min, $t_R$=13.6min, [(*R*,*R*)-enantiomer], $t_R$=20.2min [(*S*,*S*)-enantiomer]



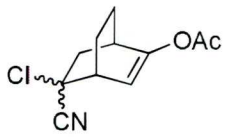

| | Name | Retention Time | Area | % Area | Height | Int Type | Peak Codes |
|---|---|---|---|---|---|---|---|
| 1 | | 13.653 | 33122106 | 49.17 | 700067 | bb | |
| 2 | | 20.237 | 34245499 | 50.83 | 523419 | bb | |

**(±)-2-hexanoxyl-bicyclo[2.2.2]octane-5-dione (248)**



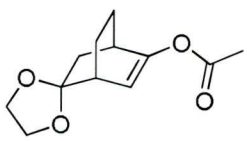
This compound was made according to the procedure for compound **247** above to give **248** as a colorless oil (138mg starting material gave 225mg product, 95% yield). $^{1}$H NMR:δ: 5.71 (dd, $J$ = 7.2Hz, $J$ = 2.8Hz, 1H), 3.15 (dt, $J$ = 7.2Hz, $J$ = 2.6Hz, 1H), 2.87 (hex, $J$ = 2.8Hz, 1H), 2.42 (t, $J$ = 7.5Hz, 2H), 2.39-2.46 (m, 1H), 2.03 (dd, $J$ = 18.0Hz, $J$ = 2.3Hz, 1H), 1.83-1.97 (m, 2H), 1.62-1.76 (m, 4H), 1.29-1.38 (m, 4H), 0.912 (t, $J$ = 7.0Hz, 3H); $^{13}$C NMR: δ: 212.0, 172.5, 156.6, 110.4, 47.9, 40.5, 37.0, 34.3, 31.6, 24.9, 24.8, 23.7, 22.7, 14.3, HRMS CI+: $C_{14}H_{21}O_3^+$, {$[M+H]^+$} Calc. 237.1491, Found 237.1492

**2-(acetoxy)-5-chloro-5-cyano-bicyclo[2.2.2]octan-2-ene (249)**



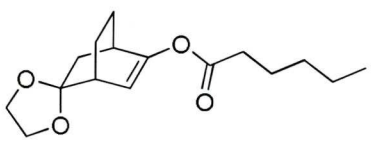

This compound was made according to the procedure for compound **247** above to give **249** as a colorless oil (180mg starting material gave 220mg product, 98% yield). $^1$H NMR:δ: 5.75 (dd, *J* = 7.0Hz, *J* = 2.0Hz, 1H), 3.21-3.25 (m, 1H), 2.68 (app. hex, *J* = 2.6, 1H), 2.54 (dd, *J* = 14.6Hz, *J* = 2.4Hz m, 1H), 2.41 (dt, *J* = 14.6Hz, *J* = 3.0Hz, 1H), 2.17 (s, 3H), 2.06-2.14 (m, 1H), 1.56-1.69 (m, 4H); $^{13}$C NMR: δ: 169.3, 153.6, 120.8, 111.8, 56.8, 45.8, 43.0, 34.5, 23.4, 23.0, 21.2; HRMS CI+: $C_{11}H_{16}ClN_2O_2^+$, {$[M+NH_4]^+$} Calc. 243.0900, Found 243.0905

**(±)-2-(acetoxy)-bicyclo[2.2.2]octan-5-{2'-[1,3-dioxolane]} (250)**



This compound was made according to the procedure for compound **247** above to give **250** as a colorless oil (182mg starting material gave 218mg product, 97% yield). $^1$H NMR:δ: 5.72 (dd, *J* = 7.3Hz, *J* = 2.5Hz, 1H), 3.86-3.95 (m, 4H), 2.64 (dt, *J* = 7.4Hz, *J* = 2.8Hz, 1H), 2.58 (app. hex, *J* = 2.7Hz), 2.13 (s, 3H), 2.01 (dt, *J* = 13.5Hz, 2.8Hz, 1H), 1.90-1.98 (m, 1H), 1.73 (dd, *J* = 13.5, *J* = 2.4Hz, 1H), 1.59-1.65 (m, 2H), 1.27-1.35 (m, 1H); $^{13}$C NMR: δ: 169.55, 155.06, 113.47, 113.29, 64.67, 64.44, 41.52, 39.01, 25.90, 23.39, 21.67, 21.25; HRMS CI+: $C_{12}H_{16}O_4Na^+$, {$[M+Na]^+$} Calc. 247.0946, Found 247.0940

**(±)-2-(hexanoyloxy)-bicyclo[2.2.2]octan-5-{2'-[1,3-dioxolane]} (251)**

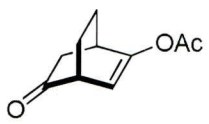


This compound was made according to the procedure for compound **247** above to give **251** (except the hexanoic anhydride was used instead of acetic anhydride) as a

colorless oil (182mg starting material gave 266mg product, 95% yield).

$^1$H NMR:δ: 5.55 (dd, $J$ = 7.4Hz, $J$ = 2.5Hz, 1H), 3.70-3.81 (m, 4H), 2.49 (dt, $J$ = 7.3Hz, $J$ = 2.8Hz, 1H), 2.23 (t, $J$ = 7.5Hz, 2H), 1.88 (dt, $J$ = 13.4Hz, 3Hz, 1H), 1.75-1.84 (m, 1H), 1.58 (dd, $J$ = 13.4Hz, $J$ = 2.4Hz), 1.40-1.55 (m, 4H), 1.07-1.24 (m, 4H), 0.74 (t, $J$ = 6.8Hz); $^{13}$C NMR: δ: 172.5, 155.2, 113.5, 113.2, 64.7, 64.4, 41.6, 39.0, 35.9, 34.4, 31.6, 25.0, 24.5, 22.7, 21.7, 14.3; HRMS CI+: $C_{16}H_{25}O_4^+$, {$[M+H]^+$} Calc. 281.1753, Found 281.1760

**(*R,R*)-(+)-2-Acetoxy-bicyclo[2.2.2]octan-2-en-5-one (247)**




**Catalyst Preparation (*Humicola* sp. Lipase on Accurel).**

The Accurel was bought from Accurel systems, AKZO Faser AG, Obernburg, Germany. In a small sample tube, Accurel (1 g) was vortexed with EtOH (3 mL), allowed to stand for 15 min, and then transferred to a 100 mL conical flask. Sodium phosphate buffer (0.1M, pH 6.0) (20 mL) and *Humicola* sp. lipase solution (200 μL) were added, and the resulting suspension was incubated at 30 °C for 48 h. The mixture was filtered through a Buchner funnel and washed with distilled water (3 × 2 mL). The water saturated Accurel-lipase (3 g) was then ready for use (generally 1 g of Accurel can hold ca. 2 g water). If the catalyst is not used immediately, it could be stored in a tightly stopped sample tube in the fridge (4 °C). Before use, the catalyst should be vortexed for several minutes to encourage any water condensed on the wall of sample tube back into the catalyst. The dry catalyst was prepared by suction filtration, incubation at 30 °C for 1 day followed by drying under vacuum (3 mmHg) overnight.

**Catalyst Preparation (*Humicola* Lipase on PhosphonicS PhosES-03).**

The PhosES series materials were gifts generously supplied by PhosphonicS Ltd, UK.

To a 100 mL conical flask containing NaPi buffer (25 mM, pH 7.0, 20 mL), PhosphonicS PhosES-03 (1 g), and *Humicola sp.* lipase solution (200 μL) was added. The resulting suspension was incubated at 30 °C for 12 h. The same workup procedure as for Accurel was applied to this mixture to give ca. 1 g of catalyst (the PhosES-03 itself contains about 40 wt % water). Storage and usage of the catalyst was as for the Accurel catalyst described above. The same procedures were applied for immobilization of CAL-B except that 10 mg of freeze-dried CAL-B was used in place of the *Humicola* sp. lipase solution. The dry catalysts were prepared by suction filtration, incubation at 30 °C for 1 day followed by drying under vacuum overnight.

**PhosES-03-Supported *Humicola* sp. Lipase-Catalyzed Resolution.**

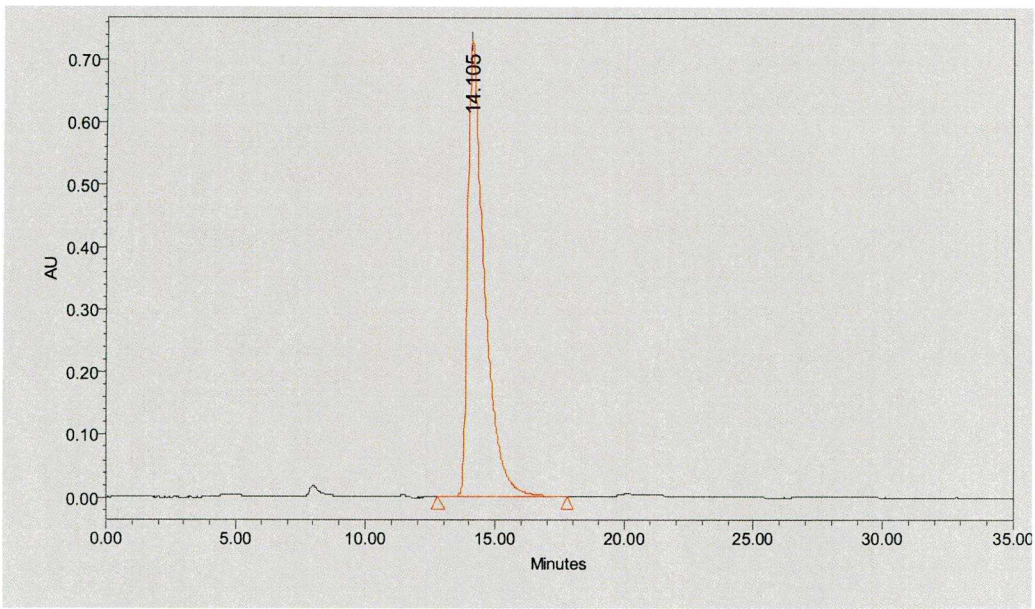
Racemic enol acetate **247** (1.0 g, 5.55 mmol) was dissolved in pentane (200 mL). To this mixture was added wet *Humicola sp.* lipase on PhosES-03 enzyme catalyst (1 g) (see above) followed by n-BuOH (10 mmol, 740 mg). The reaction finished after 1 day. The reaction was run several times and the yield of enantiomerically pure (*R,R*)-(+)-**247** varied from 320 mg to 400 mg (32- 40% yield) with 68-60% yield of diketone-**76** obtained, after chromatography (hexane/EtOAc 4:1).

**Large-Scale Resolution of (±)-13 Using Accurel-Supported *Humicola sp.* Lipase.**

A solution of (±)-2-acetoxybicyclo[2.2.2]octan-2-en-5-one **247** (9.0 g, 50 mmol), n-butanol (3.7 g, 50 mmol), and pentane (1.8 L) was added to a 3L reactor (see ***Fig. 2.3.2***) in which the immobilized enzyme (made using 8 g of Accurel, see above) was placed on a fabric-covered mesh, alongside anhydrous sodium bicarbonate (2.1 g, 20 mmol) to trap any acetic acid produced. The reaction was stirred for 50 h until the (*R,R*)-enol acetate **247** reached >99% ee. The reaction mixture was filtered through cotton wool to remove the immobilized enzyme and bicarbonate. After removal of the solvents, the residue was separated by silica-gel column chromatography (hexane-EtOAc 4:1) to give the enantiomerically pure (>99% e.e.) (*R,R*)-enol acetate **247** (3.5 g, 39% yield) and (*S,S*)-diketone-**76** (4.1 g, 59.5% yield, 64% e.e.).

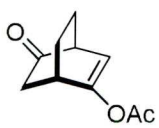
Spectroscopic data as above for racemic compound. Elemental analysis: $C_{10}H_{12}O_3$,

Calc.: C 66.65, H 6.71, Found: C 66.44, H 6.71; LRMS CI+: $[M]^+$ 180; $[\alpha]_D^{20}$ = +290 (*c* 0.34, $CHCl_3$). HPLC conditions: same as above. The absolute configuration was determined after being hydrolyzed to the corresponding diketone **7** and comparison with the literature [250].




| | Name | Retention Time | Area | % Area | Height | Int Type | Peak Codes |
|---|---|---|---|---|---|---|---|
| 1 | | 14.105 | 32317409 | 100.00 | 728864 | bb | |

**(*S,S*)-(-)-2-Acetoxy-bicyclo[2.2.2]octan-2-en-5-one (247)**

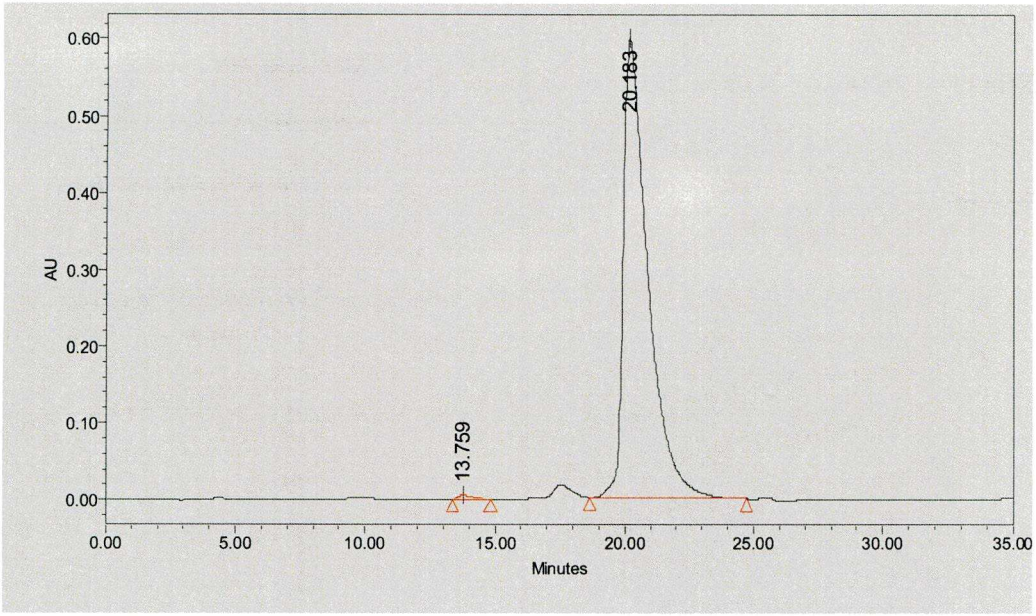



**Accurel-Supported CAL-B Lipase-Catalyzed Resolution**.

Racemic enol acetate **247** (1.0 g, 5.55 mmol) was dissolved in pentane (200 mL). To this mixture 1 g of wet type CAL-B on Accurel (see above) was added followed by n-BuOH (10 mmol, 740 mg). The reaction finished after 18 days. The reaction was run several times, and the yields of enantiomerically pure (*S,S*)-(-)-**247** varied from 280 to 300mg (28-30% yield), with 72-70% yield of diketone-**76**, obtained after chromatography (hexane/EtOAc 4:1).

Spectroscopic data as above for racemic compound. Elemental analysis: $C_{10}H_{12}O_3$, Calc.: C 66.65, H 6.71, Found: C 66.40, H 6.70; MS CI+: $[M]^+$ 180; $[\alpha]_D^{20}$ = -282 (*c*

0.40, $CHCl_3$). HPLC conditions: same as above. The absolute configuration was determined after being hydrolyzed to the corresponding diketone **7** and comparison with the literature [153].



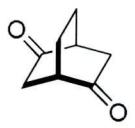

| | Name | Retention Time | Area | % Area | Height | Int Type | Peak Codes |
|---|---|---|---|---|---|---|---|
| 1 | | 13.759 | 237978 | 0.60 | 5921 | bb | |
| 2 | | 20.183 | 39495000 | 99.40 | 598303 | bb | |

**(*R,R*)-(-)-bicyclo[2.2.2]octan-2,5-dione (76)**

To a 100ml flask containing (+)-**247** (100 mg) was added NaPi buffer (50 mL, 0.1M, pH7.5) and crude *Candida rugosa* lipase (lipase AY) (5mg). The resulting mixture was stirred for 2 hr. The buffer solution was extracted with EtOAc (50 mL × 3) and the combined organic extracts dried over magnesium sulfate. Filtration and evaporation to give 76mg (100% yield) pure (*R,R*)-(-)-diketone **76** as a white solid. $[\alpha]_D^{20}$ = -43 (*c* 0.42, $CHCl_3$)

Spectroscopic data as above for racemic compound.

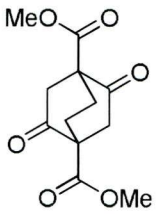
**(*S,S*)-(+)-bicyclo[2.2.2]octan-2,5-dione (76)**



Same procedure as above. Quantitative yield. Spectroscopic data as above for racemic compound. $[\alpha]_D^{20}$ = +44 (*c* 0.36, $CHCl_3$) {+50 (*c* 0.55, $CHCl_3$) in lit.[153]}

### 5.2.2 Compounds for the chemo-enzymatic synthesis of chiral 1,4-di-substituted-bicyclo[2.2.2]octane-2,5-ene ligand

**(±)-1,4-di(methoxycarbonyl)-bicyclo[2.2.2]octane-2,5-dione (254)**

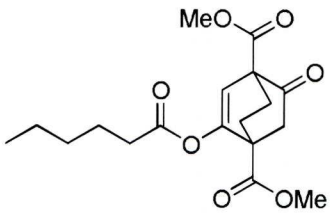



To a three-necked, $N_2$-purged flask, containing 1,2-dimethoxyethane (200 mL) was added sodium hydride (48.0 g, 60 wt%, 1.2 mol). To the resulting suspension, 1,4-di(dimethoxycarbonyl)cyclohexan-2,5-dione **253** (91.2g, 0.4 mol) was added portionwise with stirring at room temperature (control the addition rate to avoid violent reaction). After the $H_2$ bubbles ceased, the reaction mixture was heated to reflux until the color of the solid turned pink. Almost all of the solvent was removed by distillation at normal atmospheric pressure, and the residue dried under vacuum. Dibromoethane (150 mL) was added and the reaction heated at reflux overnight whereupon the dark brown color changed to pale pink.

The reaction mixture was cooled to room temperature and filtered to obtain a solid comprising product and inorganic salt. The solid was washed with water, methanol and hexane in turn to obtain pure crystalline product (71g, 70% yield).

$^1$H NMR δ 3.80 (s, 6H), 3.07 (dd, *J* = 20Hz, *J* = 3Hz, 2H), 2.73 (d, *J* = 20Hz, 2H), 2.47-2.56 (m, 2H), 2.09-2.16 (m, 2H), $^{13}$C NMR δ 203.8, 169.4, 57.8, 53.2, 42.2, 24.9; Elemental analysis: $C_{12}H_{14}O_6$, Calc. C 56.69, H 5.55, Found: C56.55, H 5.58; LRMS CI+: {$[M+NH_4]^+$} 272.

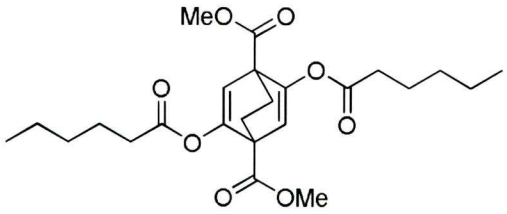
**(±)-1,4-di(methoxycarbonyl)-2-hexanoyloxy-bicyclo[2.2.2]octane-2-en-5-one (289)**




Compound (±)-**254** (38.1 g, 0.15 mol) was dissolved in anhydrous THF (400 mL) in a three-necked 1L flask and cooled to -78°C with stirring. LHMDS solution (1.06M, 162 mL, 0.172 mol) was added dropwise over 30 min. The reaction mixture was stirred at -78°C for another 30 min followed by addition of hexanoic anhydride (39.7 mL, 36.8 g, and 0.172 mol). The resultant mixture was stirred at -78°C for 30mins then warmed to room temperature. Saturated $NaHCO_3$ aq. (200 mL) was added to quench the reaction before extraction with $Et_2O$ (3 x 200 mL). The ether layers were combined and dried over anhydrous $Na_2SO_4$. Filtration and removal of the solvent by rotary evaporation gave 54 g of crude product (of which 95% is the desired product and 4% was bis-enol hexanoyl ester). The crude product can be directly used in the enzyme resolution. Re-crystallization in hexane-EtOAc gave pure product as white crystals (45 g, 85% yield).

$^1$H NMR δ 6.17 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.86 (dd, $J$ = 18.3Hz, $J$ = 3.3Hz, 1H), 2.33-2.45 (m, 4H), 2.19-2.29 (m, 1H), 1.91-2.09 (m, 2H), 1.58-1.69 (m, 2H), 1.28-1.39 (m, 4H), 0.91 (t, $J$ = 7Hz, 3H); $^{13}$C NMR δ 202.8, 172.2, 170.9, 169.7, 152.6, 112.0, 61.1, 53.1, 53.0, 50.2, 41.9, 34.1, 31.5, 30.0, 26.1, 24.6, 22.67, 14.26; Elemental analysis: $C_{18}H_{24}O_7$, Calc. C 61.35, H 6.86, Found: C61.41, H 6.90; LRMS ESI+: $[M+Na]^+$ 375.

**(±)-1,4-di(methoxycarbonyl)-2,5-di(hexanoyloxy)-bicyclo[2.2.2]octane-2-,5-diene (289a)**



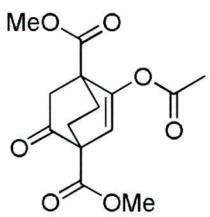
Prepared by similar procedure for compound **289**, except 2.5 eq. of LiHMDS and 2.5 eq. of hexanoyl anhydride were used, 85% yield after column.

$^1$H NMR:δ: 6.13 (s, 2H), 3.59 (s, 6H), 2.12 (t, $J$ = 9.7Hz, 4H), 1.98-2.06 (m, 2H), 1.61-1.69 (m, 2H), 1.37-1..45 (m, 4H), 1.08-1.14 (m, 8H), 0.69 (t, $J$ = 6.7 Hz, 6H)

$^{13}$C NMR: δ: 171.47, 170.90, 153.63, 116.87, 77.63, 54.23, 52.90, 34.32, 31.53, 31.35, 24.66, 22.67, 14.25

HRMS ESI+: $C_{24}H_{34}O_8Na^+$, {[M+Na]$^+$} Calc. 473.2151, Found 473.2130

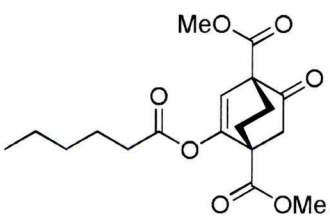
**(±)-1, 4-di(methoxycarbonyl)- 2-Acetoxyl -bicyclo[2.2.2]octane-2-en-5-one (289b)**



Prepared by the same proceedure for compound **247**, 96% yield.

1H NMR: δ: 6.18 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 2.84 (dd, $J$ = 18.3Hz, $J$ = 3.3Hz, 1H), 2.43 (d, $J$ = 18.3Hz, 1H), 2.35-2.42 (m, 1H), 2.18-2.27 (m, 1H), 2.16 (s, 3H), 1.91-2.10 (m, 2H); $^{13}$C NMR: δ: 202.8, 170.7, 169.7, 169.3, 152.5, 112.2, 61.1, 53.2, 53.0, 50.1, 41.9, 30.1, 26.1, 20.9; HRMS ESI+: $C_{14}H_{16}O_7Na^+$, {[M+Na]$^+$} Calc. 317.0794, Found 317.0800

**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2-hexanoyloxy-bicyclo[2.2.2]octan-2-en-5-one [(*S*,*S*)-(+)-289]**



Typical run for resolution

**Method A**:

The (±)-enol hexanoate **289** (40 g, 0.157mol) was dissolved in $Et_2O$ (1.5 L) and to this citrate buffer (2 L, 0.1M, pH=5.2) was added. The resulting biphasic solution was vigorously stirred and porcine pancreatic lipase (PPL) (Aldrich) (8 g) added. The reaction was monitored by HPLC (see below). The e.e. of (*S,S*)-**289** reached 95% after 2 days reaction whereupon the reaction was transferred to a separating funnel. The ethereal layer was collected and the buffer layer extracted with dichloromethane (3 x 500 ml). All organic layers were combined and washed with 0.5N NaOH aq., water and brine in turn and then dried over anhydrous $Na_2SO_4$. Filtration and rotary evaporation gave a crude colorless oil that was purified by flash column chromatography (Hexane: EtOAc; 4:1) to give (*S,S*)-**289** (13 g, 33% yield, 95% e.e.) and (*R,R*)-**254** (19 g, 65% yield, 40% e.e.).

The 13 g (95% e.e.) (*S,S*)-**289** enantiomerically enriched product was purified by crystallization of the racemate from hexane-EtOAc to give 10 g (25% yield) enantiomerically pure (*S,S*)-**289** after evaporation:

(*S,S*)-enol, ester **289** (13 g) was transferred to a 500ml flask, and hexane (300 ml) added. EtOAc was then added dropwise with stirring at room temperature until a clear solution was obtained. This solution was refrigerated (-18°C) (if necessary a racemic crystal seed of compound **289** can be added to accelerate the crystallization). In order to obtain the highest yield, the e.e. of the enol ester in solution is monitored by HPLC, after the onset of crystallization. The mixture was filtered immediately and quickly when the e.e. was 100%. The flask was washed out with pre-cooled hexane and the combined filtrates evaporated to give enantiomerically pure (*S,S*)-**289**.

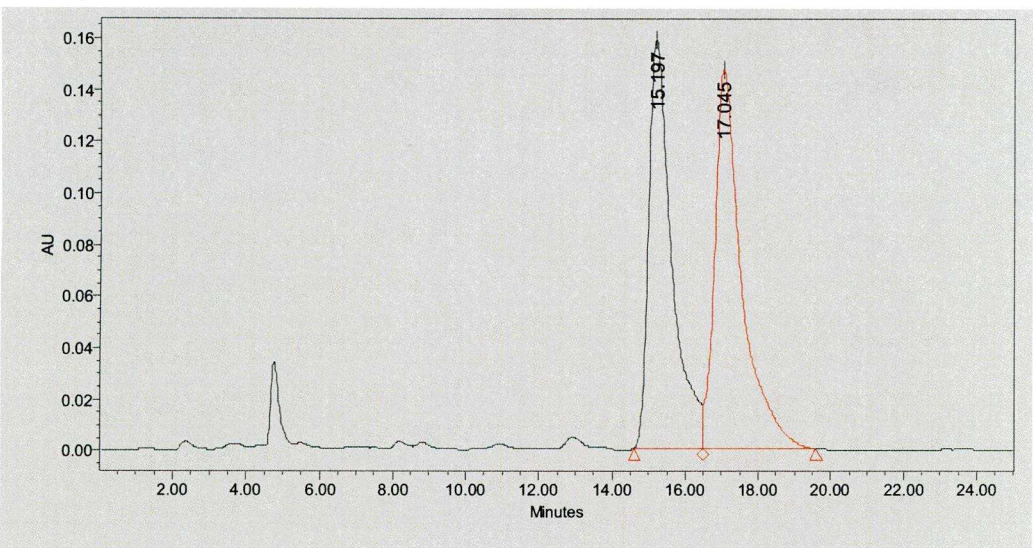
The (*R,R*)-diketone **254** can also be purified to enantiomeric purity after conversion to the hexanoyl enol ester **289** and crystallization as above, even when the initial e.e. is only 40%.

**Method B:**

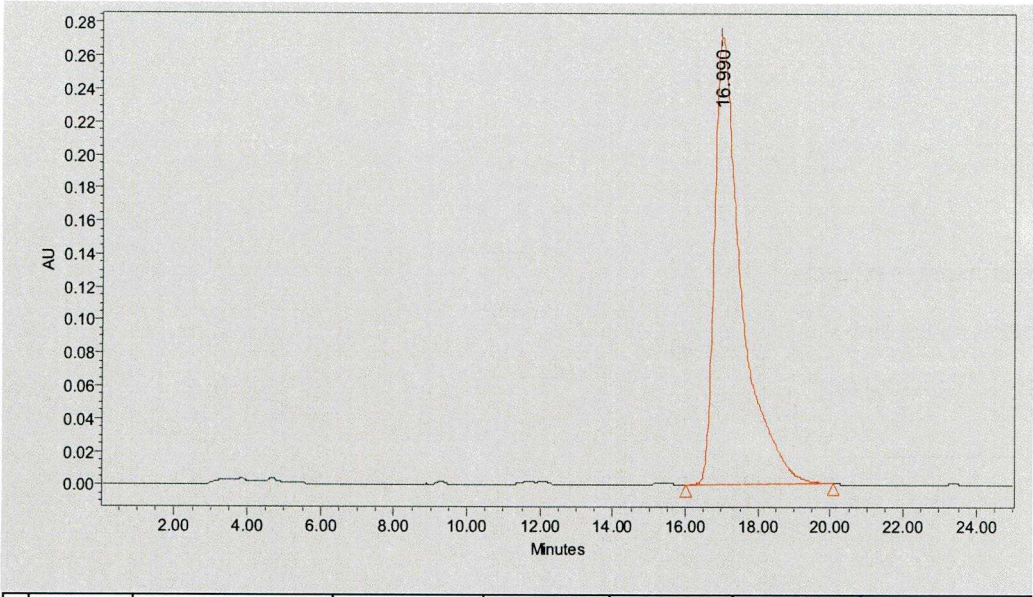
The enol hexanoate **254** (11g, 31mmol) was dissolved in $Et_2O$ (400mL) and citrate buffer (1 L, 0.1M, pH = 5.2). To this mixture PPL (2 g) was added and the reaction

stirred for 12 h. The reaction was worked-up as above to give 5.6 g of (*S,S*)-**289** (51%, 71% ee) and 5.4 g of (*R,R*)-**254** (49%, 70% ee). Purification by crystallization of 5.6 g (*S,S*)-**289** (71% ee) from hexane-EtOAc as above gave 3.8 g (35% yield) enantiomerically pure (*S, S*)-**289**.

Spectroscopic data as above for racemic compound. Elemental analysis: $C_{18}H_{24}O_7$, Calc.: C 61.35, H 6.86, Found: C61.30, H 6.85; MS ESI+: {$[M+Na]^+$} 375; $[\alpha]_D^{20}$ = +189.5 (c 0.46, $CHCl_3$). HPLC conditions: Chiracel AD column, Hexane:Isopropanol=95:5, $t_R$=15.2min, [(*R,R*)-enantiomer], $t_R$=17.1min [(*S,S*)-enantiomer]. The absolute configuration was determined by single crystal X-ray analysis of the derivative (*R,R*)-**265** (See details for characterization of compound (*R,R*)-**265**).

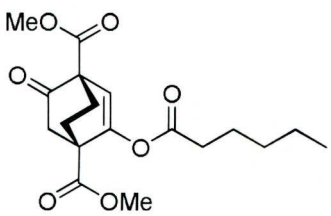



| | Name | Retention Time | Area | % Area | Height | Int Type | Peak Codes |
|---|---|---|---|---|---|---|---|
| 1 | | 15.275 | 6180364 | 47.64 | 146530 | bV | |
| 2 | | 17.121 | 6791827 | 52.36 | 137090 | vb | |



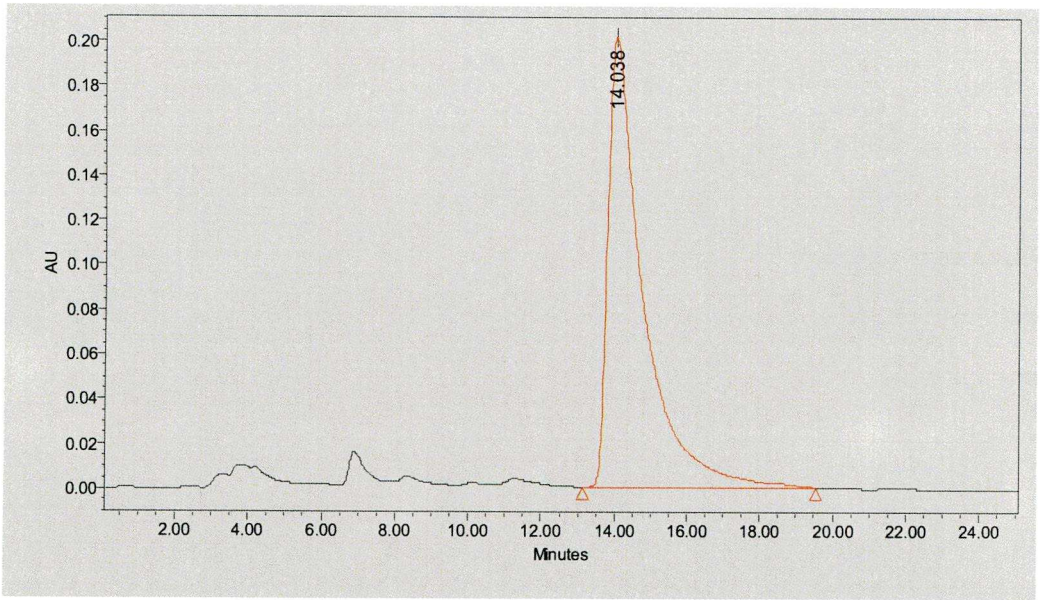

| | Name | Retention Time | Area | % Area | Height | Int Type | Peak Codes |
|---|---|---|---|---|---|---|---|
| 1 | | 16.990 | 12464142 | 100.00 | 260460 | bb | |

**(*R,R*)-(+)-1,4-di(methoxycarbonyl)-2-hexanoyloxy-bicyclo[2.2.2]octan-2-en-5-one (289)**



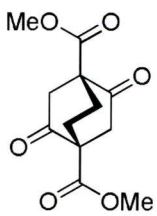

The enantiomerically pure (*R,R*)-**289** was prepare according to the follows: Through method B described above, the enantiomerically enriched diketone (*R,R*)-**254** was isolated (49% yield, 70% e.e.). This diketone (5.08g, 2mmol) was converted into its corresponding mono hexanoyl ester **289** using same procedure described before (6.70 g, 95% yield). This enantiomerically enriched (*R,R*)-**289** (6.70g, 70% e.e.) was purified to >99% e.e. by the same re-crystallization method (4.64g, 69% yield).

Spectroscopic data as above for racemic compound. Elemental analysis: $C_{18}H_{24}O_7$, Calc.: C 61.35, H 6.86, Found: C61.32, H 6.85; MS ESI+: {$[M+Na]^+$} 375; $[\alpha]_D^{20}$ = -190 (*c* 0.52, $CHCl_3$).



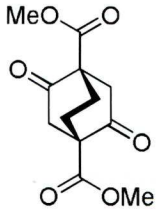

| | Name | Retention Time | Area | % Area | Height | Int Type | Peak Codes |
|---|---|---|---|---|---|---|---|
| 1 | | 14.038 | 13379009 | 100.00 | 201336 | bb | |

**(*S,S*) -(-)-1,4-di(methoxycarbonyl) bicyclo[2.2.2]octane-2,5-dione [(*S,S*)-(-)-254]**



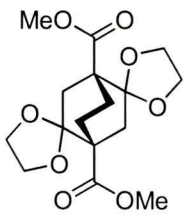

(*S,S*)-enol ester **289** (7.5 g, 21mmol) was dissolved in methanol (200 mL), $NaHCO_3$ (1.68 g, 0.02 mol) was added and the mixture stirred for 6h to give full conversion. The reaction mixture was filtered through a Celite pad, filtered and the solvent removed to give the crude product (*S,S*)-dione **254**. This was dissolved in dichloromethane, washed with water then dried over anhydrous $Na_2SO_4$. Filtration and solvent removal gave a solid-oil mixture that was subject to vacuum overnight to give pure product as a white solid (5.4 g, 99% yield). Spectroscopic data as above for (±)-**289**; Elemental analysis: $C_{12}H_{14}O_6$, Calc. C 56.69, H 5.55, Found: C56.70, H 5.57; MS CI+: $[M+NH_4]^+$ 272; $[\alpha]_D^{20}$ = -15.1 (*c* 0.47, $CHCl_3$)

**(*R,R*) -(+)-1,4-di(methoxycarbonyl) bicyclo[2.2.2]octane-2,5-dione (254)**



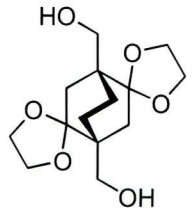
The dione (*R,R*)-**254** was prepared by the same procedure as for (*S,S*)-**254** (99% yield) Spectroscopic data as above for (±)-**254**; Elemental analysis: $C_{12}H_{14}O_6$, Calc. C 56.69, H 5.55, Found: C56.70, H 5.56; MS CI+: $[M+NH_4]^+$ 272; $[\alpha]_D^{20}$ = +15.0 (*c* 0.44, $CHCl_3$)

**(*S,S*)-(-)-1,4-di(methoxylcarbonyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (255)**



The (*S,S*)-dione **254** (1.2 g, 4.7 mmol), ethylene glycol (3.0 g, 48 mmol, 10eq.) and *p*-toluenesulphonic acid (68 mg, 0.4 mmol) were added to a 100 mL three-necked flask followed by addition of toluene (40 mL). The flask was fitted with Dean-Stark equipment and a condenser and refluxed for 12 h, then cooled to room temperature. The reaction mixture was transferred to a separating funnel, EtOAc (20ml) was added and the solution washed with 1N NaOH solution, water and brine before drying over anhydrous $Na_2SO_4$. Filtration and solvent evaporation gave the crude product that was recrystallized from hexane-EtOAc to afford pure product as white solid (1.4 g, 87%). $^1H$ NMR δ 3.93-4.00 (m, 6H), 3.73-3.77 (m, 2H), 3.68 (s, 6H), 2.45 (dd, *J* = 15Hz, *J* = 2.5Hz, 2H), 2.30-2.36 (m, 2H), 2.00 (d, *J* = 15Hz, 2H), 1.67-1.75(m, 2H); $^{13}C$ NMR δ 173.5, 110.4, 65.4, 65.2, 52.5, 49.3, 42.1, 24.4; Elemental analysis: $C_{16}H_{22}O_8$, Calc. C 56.14, H 6.48, Found: C56.19, H 6.50; LRMS ESI+: $\{[M+Na]^+\}$ 365; $[\alpha]_D^{20}$ = -40.3 (*c* 0.70, $CHCl_3$)

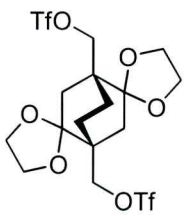
**(*R*,*R*)-(-)-1,4-Di(hydroxylmethyl)bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (256)**




In a three-necked 100ml flask, $LiAlH_4$ (360 mg, 9.6mmol) was added to THF (20 mL) and $Et_2O$ (20 mL) under nitrogen. The $LiAlH_4$ suspension was stirred at room temperature and compound (*S,S*)-**255** (1.1g, 3.2mmol) was added in three portions. The reaction mixture was warmed to 40°C and stirred for 2h.

The reaction was quenched by adding EtOAc (5mL) and then water (ca.50 mL) until there was no further effervescence. The resultant mixture was transferred to a separating funnel and extracted with dichloromethane (3 x 50 mL). All extracts were combined and washed with 1N HCl aq. solution, water, sat. $NaHCO_3$ solution and brine then dried over anhydrous $Na_2SO_4$. Filtration and removal of the solvent gave a colorless oil. Flash column chromatography (hexane:EtOAc; 3:1) gave pure product (820mg, 88% yield) which was a colorless oil that solidified under vacuum overnight. $^1H$ NMR δ 3.93-4.01(m, 8H), 3.67 (dd, $J$ = 11Hz, $J$ = 3.5Hz, 2H), 3.31 (d, $J$ = 11Hz, $J$ = 8Hz, 2H), 2.78 (dd, $J$ = 8Hz, $J$ = 3.5Hz, 2H), 2.17 (dd, $J$ = 14Hz, $J$ = 3Hz, 2H), 1.71-1.18 (m, 2H), 1.61 (d, $J$ = 14Hz, 2H), 1.24-1.33 (m, 2H); $^1H$ NMR δ 112.7, 66.4, 64.4, 64.3, 41.8, 41.3, 24.1; Elemental analysis: $C_{14}H_{22}O_6$, Calc. C 58.73, H 7.74, Found: C58.48, H 7.77; LRMS CI: $\{[M+H]^+\}$ 287; $[\alpha]_D^{20}$ = -60.6 (*c* 0.57, $CHCl_3$)

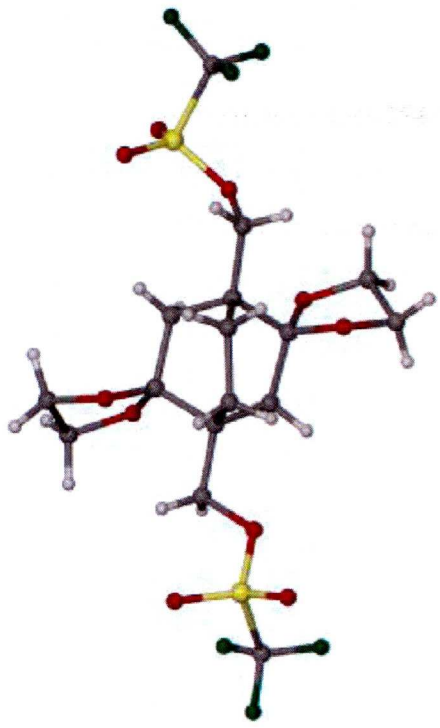
**(*R*,*R*)- (-)-1,4-di(trifluorosulphonyloxymethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (265)**




The diol (*S,S*)-**256** (200 mg, 0.70 mmol) was added to a 25ml flask containing

anhydrous dichloromethane (5 mL) and pyridine (1mL). The solution was cooled to -78°C and triflic anhydride (592 mg, 2.1 mmol) was added. The reaction was then allowed to warm to room temperature and transferred to a separating funnel to which ice-water (20 mL) was subsequently added. The mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with 1N HCl aq. solution, water and brine and dried over $Na_2SO_4$. Filtration and removal of solvents by rotary evaporation gave crude product, which was purified by flash column chromatography (Hexane:EtOAc 5:1) to give a colorless oil (360 mg, 93% yield). Crystals for X-ray analysis were obtained via re-crystallization from hexane. $^1$H NMR δ 4.45 (d, *J* = 9.6Hz, 2H), 4.37 (d, *J* = 9.6Hz, 2H), 3.90-4.02 (m, 6H), 3.80-3.88 (m, 2H), 2.06 (dd, *J* = 14Hz, *J* = 2.7Hz, 2H), 1.85 (d, *J* = 13.8Hz, 2H); 1.79-1.90 (m, 2H); 1.63-1.72 (m, 2H); $^{13}$C NMR δ 120.6, 117.4, 109.5, 79.0, 64.9, 64.7, 42.0, 40.4, 22.8 (the quartet for $CF_3$ carbon was not seen ). Elemental analysis: $C_{16}H_{20}F_6O_{10}S_2$, Calc. C 34.91, H 3.66, Found: C34.93, H 3.69; HRMS ESI+: $C_{16}H_{20}F_6O_{10}S_2Na$, {$[M+Na]^+$} Calc.: 573.0300; Found: 573.0304; $[\alpha]_D^{20}$ = -12.4 (*c* 0.41, $CHCl_3$).

## Single crystal diffraction:

| *Crystal and Refinement Data* | |
|---|---|
| $C_{16}H_{20}F_6O_{10}S_2$<br>$M = 550.44$<br>yellow prism, 0.50 0.40 0.30 $mm^3$<br>orthorhombic, $P2_12_12_1$ (No. 19)<br>$a = 5.9914(5)$ Å<br>$b = 18.001(2)$ Å<br>$c = 19.852(2)$ Å<br>$V = 2141.1(3)$ $Å^3$,<br>$Z = 4$,<br>$D_c = 1.708$ $g/cm^3$<br>$T = 100(2)$K<br>MoK radiation, $= 0.71073$ Å,<br>2 $_{max} = 54.9°$<br>12789 reflections collected, 4731 unique<br>$R_{int} = 0.0271$<br>Final *GooF* = 1.137<br>*R1* = 0.0362, *R2* = 0.0765<br>387 parameters, 0 restraints<br>Absolute structure parameter = 0.0(1)<br>$= 0.095$ $mm^{-1}$ |  |

**Data collection, structure solution and refinement**

A suitable crystal was selected from a sample submitted by Y. Luo from the research group of Dr. A. Carnell. The crystal was mounted on a glass fibre and placed in a cold stream at 100K. Single crystal X-ray data were collected on a Bruker D8 diffractometer with an APEX CCD detector, and 1.5 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Exposure times of 20 s per frame and scan widths of 0.3° were used throughout the data collection. The data collection was performed using three $\omega$ scans yielding data in the $\theta$ range 1.53 to 27.5° with an average completeness of 99%. The frames were integrated with the SAINT v6.45a (Bruker, 2005).[1] A semi-empirical absorption correction using multiple-reflections was carried out using the program SADABS V2008-1 (Bruker, 2008)[2], that implements an algorithm published by Blessing[3]. The structure was solved and refined with X-SEED,[4] a graphical interface to SHELX97 (Sheldrick, 1997).[5] In the final cycles of refinement all

[1] Bruker (2005). SAINT V6.45a, BRUKER AXS Inc., Madison, WI, USA.

[2] Bruker (2008), SADABS V2008-1, BRUKER AXS Inc., Madison, WI, USA.

[3] Blessing, R. H. *Cryst. Rev.* **1987**, *1*, 3-58; Blessing, R. H. (1989) *J. Appl. Cryst.* **1989**, *22*, 396-397.

[4] Barbour, L. J. "X-Seed – A software tool for supramolecular crystallography" *J. Supramol. Chem.* **2001**, *1*, 189-191.

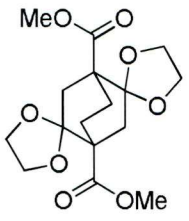
[5] Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

non-hydrogen atoms were refined anisotropically, and the hydrogen atoms refined freely.

Table 1. Crystal data and structure refinement for YF001M.

| | | |
|---|---|---|
| Identification code | yf001m | |
| Empirical formula | C16 H20 F6 O10 S2 | |
| Formula weight | 550.44 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P212121 | |
| Unit cell dimensions | a = 5.9914(5) Å | = 90°. |
| | b = 18.0013(16) Å | = 90°. |
| | c = 19.8516(17) Å | = 90°. |
| Volume | 2141.1(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.708 $Mg/m^3$ | |
| Absorption coefficient | 0.354 $mm^{-1}$ | |
| F(000) | 1128 | |
| Crystal size | 0.50 x 0.40 x 0.30 $mm^3$ | |
| Theta range for data collection | 1.53 to 27.46°. | |
| Index ranges | -7<=h<=7, -23<=k<=20, -25<=l<=24 | |
| Reflections collected | 12789 | |
| Independent reflections | 4731 [R(int) = 0.0271] | |
| Completeness to theta = 27.46° | 99.2 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9013 and 0.8429 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4731 / 0 / 387 | |
| Goodness-of-fit on $F^2$ | 1.137 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0362, wR2 = 0.0765 | |
| R indices (all data) | R1 = 0.0388, wR2 = 0.0775 | |
| Absolute structure parameter | 0.00(6) | |
| Largest diff. peak and hole | 0.369 and -0.278 $e.Å^{-3}$ | |

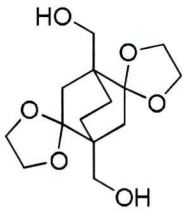
**(±)-1,4-di(methoxylcarbonyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (255)**




Prepared according to the same procedure for compound (*S,S*)-**255** (40.6 g starting material gave 46 g product, 85% yield).

Spectroscopic data as above for (*S,S*)-**255**.

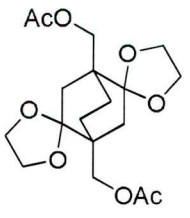
**(±)-1,4-Di(hydroxylmethyl)-Bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (256)**




Prepared according to the same procedure for compound (*R,R*)-**256** (13.7 g starting material gave 10.2 g product, 90% yield).

Spectroscopic data as above for (*R,R*)-**256**.

**(±)-1,4-Di(Acetoxylmethyl)-Bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (277)**

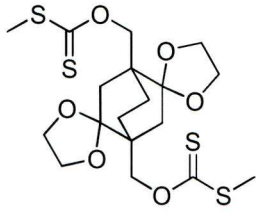



To a 25ml flask, pyridine (5ml) and 1,4-di(hydroxylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} **256** (1mmol, 286mg) were added and stirred in an ice-water bath. To this mixture acetyl chloride (2.5mmol, 196.2mg, 178 L) was added and the temperature of the reaction mixture was allowed to raise to room temperature for 6hrs. The reaction mixture was poured into an flask containing ice, which was followed by extraction EtOAc (50ml × 3). The combined

organic layer was washed with 5% HCl (20ml × 3), water and brine in turn and then dried over anhydrous magnesium sulphate. Filtration followed by evaporation of the solvent gave crude product which was purified through a short silica pad washing with Hexane – EtOAc 4 : 1 mixture as eluents. (365mg, 98% yield).

$^1$H NMR:δ: 3.80-4.06 (m, 12H); 2.05(m, 6H), 2.00 (dd, $J$ = 14Hz, $J$ = 2.6Hz, 2H), 1.82 (d, $J$ = 14Hz, 2H), 1.59-1.77 (m, 4H); $^{13}$C NMR: δ: 171.7, 110.6, 66.3, 65.1, 64.9, 41.8, 41.7, 23.4, 21.4; HRMS ESI+: $C_{18}H_{26}O_8Na$, {$[M+Na]^+$} Calc.: 393.1525; Found: 393.1536

**(±)-1,4-Dixanthoxyl-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (263)**

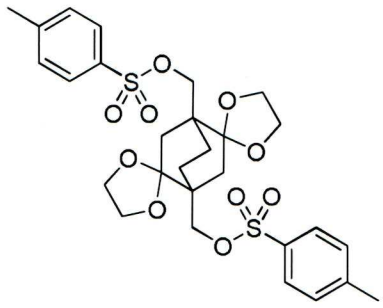


The racemic diol **256** (286 mg, 1 mmol) was dissolved in anhydrous THF (10ml) in a Schlenck reaction tube and stirred at room temperature. To this solution NaH (95 mg, 60 wt% in mineral oil, 2.5 mmol) was added followed by addition of $CS_2$ (190mg, 151 L, 2.5 mmol) and then stirred for 30min. To the resulting mixture MeI (352 mg, 154 L, 2.5 mmol) was added. The reaction finished after 5min and was quenched with water then extracted with $Et_2O$ (40 mL). The organic solution was washed with brine and dried over $Na_2SO_4$. Filtration and removal of solvents by rotary evaporation gave crude product which was purified by flash column chromatography (hexane:EtOAc; 4:1) to give **263** (396mgs, 85%).

$^1$H NMR:δ: 4.51 (d, $J$ = 11Hz, 2H), 4.46 (d, $J$ = 11Hz, 2H), 3.90-4.04 (m, 6H), 3.79-3.88 (m, 2H), 2.56 (s, 6H), 2.11 (dd, $J$ = 14Hz, $J$ = 2.6Hz, 2H), 1.88 (d, $J$ = 14Hz, 2H), 1.81-1.94 (m, 2H), 1.66-1.76 (m, 2H); $^{13}$C NMR: δ: 216.4, 110.4, 100.0, 76.0,

65.2, 65.0, 42.4, 41.9, 23.8, 19.3; HRMS, ESI+: $C_{18}H_{26}O_6S_4Na$, {$[M+Na]^+$}, Calc.: 489.0510, Found: 489.0516.

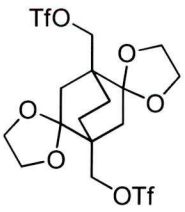
**(±)-1,4-Di(tosyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (264)**



Compound **264** was prepared by a similar procedure used for **277**, except that tosyl chloride was used instead of acetyl chloride. 1mmol starting material gave 594 mg product (quantitative yield).

$^1$H NMR:δ: 7.67 (d, $J$ = 8.2Hz, 4H), 7.26 (d, $J$ = 8.2Hz, 4H), 3.59-3.95 (m, 12H), 2.38 (s, 6H), 1.76 (d, $J$ = 14Hz, 2H), 1.69 (d, $J$ = 14Hz, 2H), 1.54 (s, 2H), 1.47 (s, 2H); $^{13}$C NMR: δ: 143.7, 131.8, 128.8, 126.8, 108.5, 70.8, 63.4, 63.1, 40.4, 39.3, 21.5, 20.6; HRMS, ESI+: $C_{28}H_{34}O_{10}S_2Na$, {$[M+Na]^+$}, Calc.: 617.1491, Found: 617.1488.

**(±)-1,4-di(trifluorosulphonyloxymethyl)bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane] (265)**

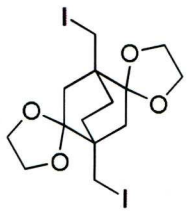



Prepared according the same procedure for (*R,R*)-**265** (2.86 g starting material gave 5.2 g product, 95% yield)

$^1$H NMR:δ: 4.45 (d, $J$ = 9.7Hz, 2H), 4.37 (d, $J$ = 9.7Hz, 2H), 3.90-4.02 (m, 6H), 3.80-3.88 (m, 2H), 2.06 (dd, $J$ = 14Hz, $J$ = 2.7Hz, 2H), 1.85 (d, $J$ = 14.0 Hz, 2H); 1.79-1.90 (m, 2H); 1.63-1.72 (m, 2H); $^{13}$C NMR: δ: 109.5, 79.0, 64.9, 64.7, 42.0, 40.4,

22.8 (the carbon in trific group was not seen due to the low concentration); ESI+: $C_{16}H_{20}F_6O_{10}S_2Na^+$ {[M+Na]$^+$}, Calc.: 573.0300, Found: 573.0292.

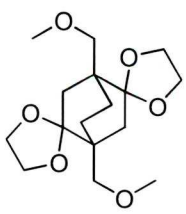
**(±)-1,4-Diiodo-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (266)**



The ditriflate **265** (550mg, 1.0 mmol) was dissolved into acetone (20ml), followed by addition of NaI (10mmol, 1.5gram). The resulting mixture was refluxed for 2hr. The acetone was removed and the resulting solid was rinsed with diethyl ether and filtered through a celite pad. Removal of the diethyl ether gave pure product **266** as a white solid (500mg, 99% yield).

$^1$H NMR:δ: 3.81-3.98 (m, 6H), 3.70-3.79 (m, 2H), 3.20 (d, $J$ = 10Hz, 2H), 3.16 (d, $J$ = 10Hz, 2H),1.89 (d, $J$ = 14Hz, 2H), 1.80 (dd, $J$ = 14Hz, $J$ = 2.7Hz, 2H), 1.61-1.72 (m, 2H), 1.48-1.58 (m, 2H); $^{13}$C NMR: δ: 109.9, 65.3, 65.0, 44.7, 42.0, 27.7, 15.2, HRMS ESI+: $C_{14}H_{20}I_2O_4Na$, {[M+Na]$^+$} Calc.: 573.9349; Found: 573.9355

**(±)-1,4-di(methoxylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (267a)**

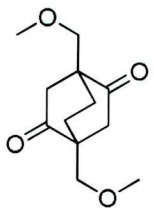


The racemic diol **256** (5.72 mg, 20 mmol) was dissolved in anhydrous THF (10ml) in a Schlenck reaction tube and stirred at room temperature. To this solution, NaH (2 g, 60 wt% in mineral oil, 50 mmol) was added followed by addition of MeI (7 g, 3.1 mL, 50 mmol) and then stirred at 40°C for 1hr. The reaction was quenched with water then extracted with $Et_2O$ (200 mL). The organic solution was washed with brine and dried over $Na_2SO_4$. Filtration and removal of solvents by rotary evaporation gave crude product which was purified by flash column chromatography (hexane:EtOAc; 4:1) to

give **267a** (6.0 g, 95%).

$^1$H NMR:δ: 3.83-3.97 (m, 6H), 3.74-3.78 (m, 2H), 3.3 (s, 6H), 3.28 (d, $J$ = 9Hz, 2H), 3.22 (d, $J$ = 9Hz, 2H), 1.91 (d, $J$ = 14Hz, 2H), 1.85 (d, $J$ = 14Hz, 2H), 1.60-1.68 (m, 4H); $^{13}$C NMR: δ: 111.3, 75.0, 65.0, 64.6, 60.0, 42.5, 41.7, 23.9; Element Analysis: Calc.: C 61.13, H 8.34, Found: C 63.20, H 8.34; HRMS, ESI+: $C_{16}H_{26}O_6Na$, {$[M+Na]^+$}, Calc.: 314.1729, Found: 314.1733.

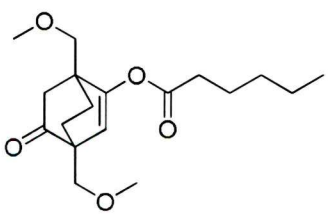
**(±)-1,4-di(methoxylmethyl)-bicyclo-[2.2.2]octan-2,5-di-one (268a)**



Diketal **267a** (4.71 g, 15 mmol) was dissolved into THF (100 ml). To this solution, of 20% HCl aqueous solution (10 ml) was added and then stirred for 12 hrs. The reaction mixture was subjected to rotary evaporation to remove the majority of the THF. The residue obtained was diluted with EtOAc (200 ml) and transferred to a separating funnel. After washing with water, saturated $NaHCO_3$ solution and brine in turn, the organic layer was dried over $MgSO_4$. Removal of the solvents gave the product which was pure enough without further purification (3.2 g, 96% yield)

$^1$H NMR:δ: 3.52 (dd, $J$ = 10Hz, $J$ = 4Hz, 2H), 3.37 (dd, $J$ = 10Hz, $J$ = 4Hz, 2H), 3.36(s, 6H), 2.62 (dd, $J$ = 19Hz, $J$ = 4Hz, 2H), 2.42 (dd, $J$ = 19, $J$ = 4Hz, 2H), 1.98-2.10 (m, 2H), 1.76-1.84 (m, 2H); $^{13}$C NMR: δ: 211.0, 73.3, 59.9, 50.6, 43.2, 25.5; Element Analysis: Calc.: C 63.70, H 8.02, Found: C 63.60, H 8.05; LRMS: {$[M+NH_4]^+$}, 244.

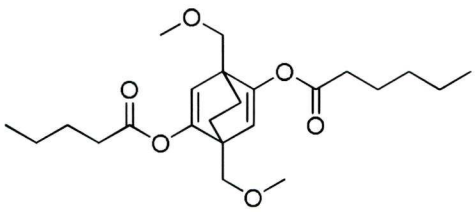
**(±)-1,4-di(methoxylmethyl)-2-hexanoyloxy-bicyclo-[2.2.2]octan-2-en-5-one (271b)**



Compound **(±)-271b** was made according to the same procedure for **289** (2.2 g starting material gave 3.0 g product, 97% yield).

$^1$H NMR:δ: 5.75 (s, 1H), 3.71 (d, $J$ = 9.6Hz, 1H), 3.51 (d, $J$ = 9.6Hz, 1H), 3.48 (d, $J$ = 9.4Hz, 1H), 3.42 (d, $J$ = 9.4Hz, 1H), 3.40 (s, 3H), 3.35(s, 3H), 2.42 (t, $J$ = 7.4Hz, 2H), 2.35 (dd, $J$ = 18.2Hz, $J$ = 2.3Hz, 1H), 2.08 (d, $J$ = 18Hz, 1H), 1.62-1.91 (m, 6H), 1.29-1.41 (m, 4H), 0.91 (t, $J$ = 7Hz, 3H); $^{13}$C NMR: δ: 210.2, 172.3, 154.7, 114.3, 77.4, 74.1, 72.6, 60.0, 59.8, 54.0, 44.4, 43.7, 34.4, 31.6, 29.2, 26.8, 24.9, 22.7, 14.3; HRMS, CI+: $C_{18}H_{29}O_5$, {$[M+H]^+$}, Calc.: 325.2015, Found: 325.2017.

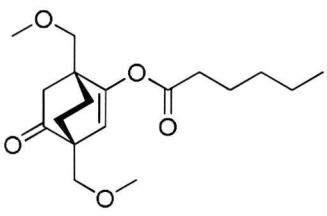
**(±)-1,4-di(methoxylmethyl)-2,5-di(hexanoxyl)-bicyclo[2.2.2]octan-2,5-diene (271c)**



This compound **271c** was made according to the same procedure used for **289a** (220 mg starting material gave 336 mg product, 84 % yield).

$^1$H NMR:δ: 5.83 (s, 2H), 3.60 (d, $J$ = 9.3Hz, 2H), 3.52 (d, $J$ = 9.3Hz, 2H), 3.30 (s, 6H), 2.28 (t, $J$ = 7.4Hz, 4H), 1.47-1.70 (m, 8H), 1.16-1.28 (m, 8H), 0.80 (m, 6H), $^{13}$C NMR: δ: 172.0, 155.9, 119.1, 73.5, 59.8, 47.9, 34.5, 31.6, 30.6, 24.9, 22.8, 14.2; HRMS, ESI+: $C_{23}H_{36}O_6Na$, {$[M+Na]^+$}, Calc.: 431.2410, Found: 431.2415.

**(*R,R*)-1,4-di(methoxylmethyl)-2-Hexanoxyl-bicyclo-[2.2.2]octan-2-en-5-one (271b)**



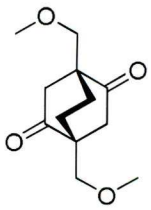
This compound was obtained from lipase resolution.

Racemic enol hexanoyl ester **271b** (750 mg, 2.4 mmol) was dissolved into DMF (12

ml). With vigorous stirring, NaPi buffer (40ml, 0.1 M, pH 7.0) was poured into this solution. To the resulting mixture, PPL (20 mg) was added and the reaction was monitored by chiral HPLC until (*R,R*)-**271b** was >99% e.e. The reaction was extracted with diethyl ether (50 ml × 4). The combined ethereal layer was washed with 0.5 M NaOH solution, water and brine in turn then dried over anhydrous $MgSO_4$. Removal of solid by filtration and solvent by evaporation followed by chromatography gave enantiomerically pure (*R,R*)-**271b** (188 mg, 25% yield) and enantiomerically enriched (*S,S*)-**268a** (387 mg, 74% yield)

$^1$H NMR:δ: 5.75 (s, 1H), 3.71 (d, *J* = 9.7Hz, 1H), 3.51 (d, *J* = 9.7Hz, 1H), 3.46 (d, *J* = 9.Hz; 1H), 3.40 (d, *J* = 9.Hz; 1H), 3.40 (s, 3H); 3.35 (s, 3H), 2.42 (t, *J* = 7.4Hz), 2.35 (dd, *J* = 18.1Hz, *J* = 2Hz, 1H), 2.08 (d, *J* = 18Hz, 1H), 1.62-1.91 (m, 6H), 1.29-1.41 (m, 4H), 0.91(t, *J* = 7Hz, 3H); $^{13}$C NMR: δ: 210.2, 172.3, 154.7, 114.3, 77.4, 74.2, 72.6, 60.0, 59.8, 54.0, 44.4, 43.7, 34.4, 31.6, 29.2, 26.9, 24.9, 22.7, 14.3; HRMS, ESI+: $C_{18}H_{28}O_5Na$, {$[M+Na]^+$}, Calc.: 347.1834, Found: 347.1830.

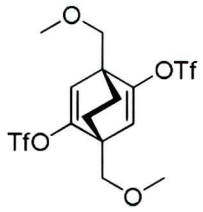
**(*R, R*)-1,4-di(methoxylmethyl)-bicyclo[2.2.2]octan-2,5-dione (268a)**



This compound **268a** was made according to the same procedure as that for (*R,R*)-**254** (320 mg starting material gave 220 mg product, 99 % yield).

Spectroscopic data as for (±)-**263a**; HRMS, ESI+: $C_{12}H_{18}O_4Na$, {$[M+Na]^+$}, Calc.: 249.1103, Found: 249.1106.

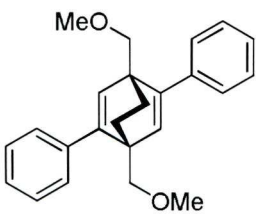
**(*R,R*)-1,4-di(methoxylmethyl)-2,5-di-(trifluoromethylsulfonyloxy)-bicyclo[2.2.2]octan-2,5-diene (273)**




This compound (*R,R*)-**273** was made according to the same procedure reported in literature [101] (220mg starting material gave 333mg product 68% yield).

$^1$H NMR:δ: 6.09 (s, 2H); 3.71 (d, *J* = 9.5Hz, 2H); 3.63 (d, *J* = 9.5Hz, 2H); 3.37 (s, 6H); 1.70-1.76 (m, 2H); 1.52-1.69 (m, 2H); $^{13}$C NMR: δ: 153.3, 120.8, 117.3 (q, *J* = 318 Hz), 70.4, 58.3, 48.2, 28.3; HRMS ESI+: $C_{14}H_{16}F_6O_8S_2Na^+$ {[M+Na]$^+$}, Calc.: 513.0088, Found: 513.0097.

**(*S,S*)-(+)-1,4-Di(methoxyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (274)**



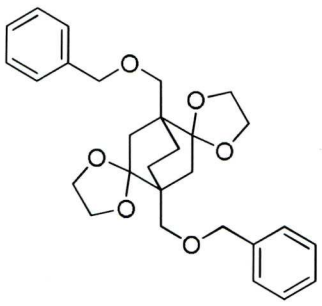

(*S,S*)-**274** was made from (*R,R*)-**273** by the same procedure described for (*S,S*)-**296** (300 mg starting material gave 200mgs (*S,S*)-**(+)-274**, 95%).

$[\alpha]_D^{20}$ = +71.8° (*c* 0.46, $CHCl_3$);

$^1$H NMR δ 7.11-7.33 (m, 10H), 6.25 (s, 2H), 3.73 (d, *J* = 9.6Hz, 2H), 3.60 (d, *J* = 9.6Hz, 2H), 3.21 (s, 6H), 1.69-1.76 (m, 2H), 1.54-1.61 (m, 2H), $^{13}$C NMR δ 149.7, 139.8, 135.3, 128.6, 128.0, 127.0, 75.8, 59.5, 50.0, 31.1; HRMS ESI+: $C_{24}H_{26}O_2Na^+$ {[M+Na]$^+$}, Calc.: 369.1831, Found: 369.1827.

**(±)-1,4-di(benzyloxylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]}**

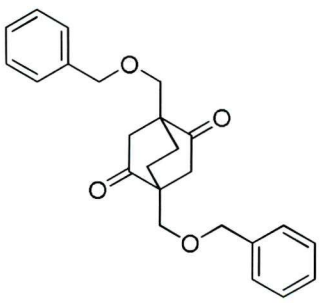
**(267b)**



This compound **267b** was made according to the same procedure used for **267a** (benzylbromide was used instead of methyliodide, 286 mg starting material gave 334 mg, 95% yield).

$^1$H NMR:δ:7.20-7.40 (m, 10H), 4.47 (s, 4H), 3.86-3.95 (m, 4H), 3.78-3.84 (m, 2H), 3.69-3.75 (m, 2H), 3.39 (d, $J$ = 8.8Hz, 2H), 3.33 (d, $J$ = 8.8Hz, 2H), 1.92-1.99 (m, 4H), 1.70-1.79 (m, 4H); $^{13}$C NMR: δ: 139.4, 128.6, 127.7, 127.6, 111.4, 100.0, 73.9, 72.4, 65.0, 64.7, 42.8, 41.9, 23.9; HRMS ESI+: $C_{28}H_{34}O_6Na^+$ {[M+Na]$^+$}, Calc.: 489.2253, Found: 489.2260.

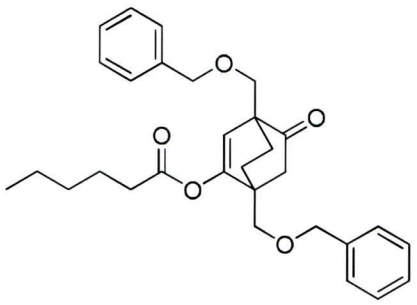
**(±)-1,4-di(benzyloxylmethyl)-bicyclo[2.2.2]octan-2,5-dione (268b)**



This compound was made according to the same procedure with **268a** (300 mg starting material gave 240 mg product, 99% yield)

$^1$H NMR:δ:7.20-7.50 (m, 10H), 4.55 (d, $J$ = 12Hz, 2H), 4.51 (d, $J$ = 12Hz, 2H), 3.61 (d, $J$ = 10Hz, 4H), 3.46 (d, $J$ = 10Hz, 4H), 2.69 (d, $J$ = 19Hz, 2H), 2.43 (dd, $J$ = 19Hz, $J$ = 2.6, 2H), 2.05-2.13 (m, 2H), 1.73-1,83 (m, 2H), $^{13}$C NMR: δ: 211.1, 138.5, 128.8, 128.1, 127.9, 77.6, 73.9, 70.7, 50.7, 43.2, 25.6; HRMS ESI+: $C_{24}H_{26}O_4Na^+$ {[M+Na]$^+$}, Calc.: 401.1729, Found: 401.1724.

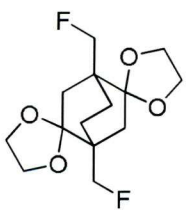
**(±)-1,4-di(benzyloxylmethyl)-2-hexanoyloxy-bicyclo[2.2.2]octan-2-en-5-one (272)**



This compound **272** was made according to the same procedure used for **289** (189 mg starting material gave 226 mg product, 95% yield)

$^1$H NMR:δ: 7.26-7.36 (m, 10H), 5.78 (s, 1H), 4.60 (d, $J$ = 12Hz, 2H), 4.56 (d, $J$ = 12Hz, 2H), 4.52 (s, 2H), 3.80 (d, $J$ = 10Hz, 2H), 3.50 (d, $J$ = 10Hz, 2H), 3.58 (t, $J$ = 10Hz, 2H), 2.40 (dd, $J$ = 18Hz, 2Hz), 2.34 (t, $J$ = 7.5Hz, 3H), 2.13 (d, $J$ = 18Hz, 1H), 1.90-1.97 (m, 1H); 1.78-1.84 (m, 2H), 1.66-1.72 (m, 1H), 1.60-1.65 (m, 2H), 1.25-1.35 (m, 4H), 0.89 (t, $J$ = 7.0Hz, 3H); $^{13}$C NMR: δ: 210.3, 172.3, 154.7, 138.7, 138.5, 126.8, 128.8, 128.1, 127.9, 127.7, 114.5, 74.0, 73.9, 71.8, 70.1, 54.1, 44.4, 43.8, 34.3, 31.6, 29.4, 27.0, 24.8, 22.7, 14.30; HRMS ESI+: $C_{30}H_{36}O_5Na^+$ {$[M+Na]^+$}, Calc.: 499.2460, Found: 499.2466.

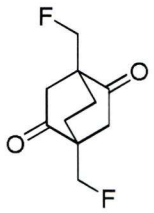
**(±)-1,4-di-(fluoromethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (269)**



This compound **269** was made according to the same procedure used for (*S,S*)-**291** (4.40 g starting material gave 2.30 g product, 99% yield).

$^1$H NMR:δ: 4.41 (dd, $J_{H\text{-}F}$ = 17.5Hz, $J$ = 9Hz, 2H), 4.39 (dd, $J_{H\text{-}F}$ = 17.5Hz, $J$ = 9Hz, 2H), 3.86-4.02 (m, 6H), 3.70-3.82 (m, 2H), 2.03 (dd, $J$ = 14Hz, $J$ = 2.6Hz, 2H), 1.82 (d, $J$ = 14Hz), 1.76-1.87 (m, 2H), 1.58-1.67 (m, 2H); $^{13}$C NMR: δ: 110.5 (d, $J$ = 5Hz), 85.1, 85.7, 77.6, 64.9 (d, $J$ = 7.5Hz), 40.8, 42.7 (d, $J$ = 7Hz), 22.8 (d, $J$ = 4Hz); ESI+: $C_{14}H_{20}F_2O_4Na^+$ {$[M+Na]^+$}, Calc.: 313.1277, Found: 313.1281.

**(±)-1,4-di(fluoromethyl)-bicyclo[2.2.2]octan-2,5-dione (270)**



This compound **270** was made according to the same procedure used for **268a** (2.0 g starting material gave 1.38 g product, 99% yield).

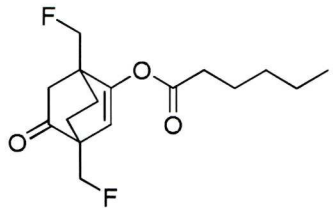
1H NMR:δ: 4.60 (dd, $J_{H\text{-}F}$ = 48Hz, $J$ = 9.9Hz, 2H); 4.50 (dd, $J_{H\text{-}F}$ = 48Hz, $J$ = 9.9Hz, 2H); 2.68 (d, $J$ = 19.4Hz, 2H), 2.55 (dd, $J$ = 19.3Hz, $J$ = 2.7Hz, 2H), 2.05-2.14(m, 2H), 1.90-2.00(m, 2H); $^{13}$C NMR: δ: 208.4, 84.6, 82.9, 50.4 (d, $J$ = 19Hz), 42.0 (d, $J$ = 2Hz), 24,3 (d, $J$ = 4Hz); ESI+: $C_{10}H_{12}F_2O_2Na^+$ {[M+Na]$^+$}, Calc.: 225.0703, Found: 225.0706.

**(±)-1,4-di(fluoromethyl)-2-acetoxyl-bicyclo[2.2.2]octan-2-en-5-one (275)**

Compound **275** was made according to the same procedure used for **247** (101 mg starting material gave 1.20 g product, 99% yield).

$^1$H NMR:δ: 5.80 (d, $J$ = 10Hz, 1H), 4.3-4.8 [two different doublets of an AB quartet, 4.73 (dd, $J_{H\text{-}F}$ = 47Hz, $J$ = 9.7Hz, 1H ), 4.55 (dd, $J_{H\text{-}F}$ = 47Hz, $J$ = 9.7Hz, 1H), 4.47 (dd, $J_{H\text{-}F}$ = 47Hz, $J$ = 9.7Hz, 1H), 4.44 (dd, $J_{H\text{-}F}$ = 47Hz, $J$ = 9.7Hz, 1H)], 2.35 (dd, $J$ = 18Hz, $J$ = 2.2Hz, 1H), 2.13 (s, 3H), 2.03 (d, $J$ = 18Hz, 1H), 1.65-1.85 (m, 4H); $^{13}$C NMR: δ: 206.3 (d, $J$ = 4Hz), 167.7, 152.6, 111.72 (d, $J$ = 5.7Hz), 82.95 (d, $J$ = 74Hz), 81.24 (d, $J$ =72Hz), 52.36 (d, $J$ = 19Hz), 43.0 (d, $J$ = 19Hz), 40.7 (d, $J$ = 4.8Hz), 26.47 (d, $J$ = 5.6Hz), 24.3 (d, $J$ = 4.0Hz), 19.7; ESI+: $C_{12}H_{14}F_2O_3Na^+$ {[M+Na]$^+$}, Calc.: 267.0809, Found: 225.0805.

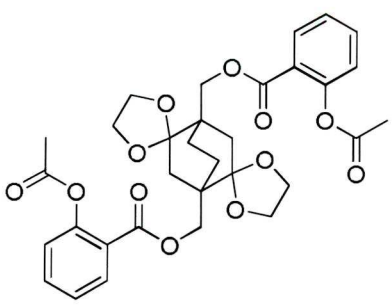
**(±)-1,4-di(fluoromethyl)-2-hexanoyloxy-bicyclo[2.2.2]octan-2-en-5-one (276)**



This compound **276** was made according to the same procedure with **289** (1.01 g starting material gave 1.44 g product, 96% yield).

$^1$H NMR:δ: 5.70 (s, 1H), 4.61 (dd, $J_{H\text{-}F}$ = 70Hz, $J$ = 9.7Hz, 1H), 4.48 (dd, $J_{H\text{-}F}$ = 70Hz, $J$ = 9.7Hz, 1H), 4.41 (dd, $J_{H\text{-}F}$ = 21.9Hz, $J$ = 9.6Hz, 1H), 4.30 (dd, $J_{H\text{-}F}$ = 21.9Hz, $J$ = 9.6Hz, 1H), 2.29 (t, $J$ = 7.4Hz, 2H), 2.28-2.30 & 2.23-2.26 (m, 1H), 1.95 (d, $J$ = 18Hz, 1H), 1.59-1.79 (m, 4H), 1.68-1,57 (m, 2H), 1.14-1.25 (m, 4H), 0.72-0.79 (m, 3H); $^{13}$C NMR: δ: 207.7 (d, $J$ = 5Hz), 172.1, 154.2, 113.0 (d, $J$ = 5.7Hz), 84.4 (d, $J$ = 73Hz), 82.8 (d, $J$ =70Hz), 53.8 (d, $J$ = 19Hz), 44.5 (d, $J$ = 19Hz), 42.2 (d, $J$ = 3.5Hz), 34.4, 31.5, 27.9 (d, $J$ = 5.6Hz), 25.8 (d, $J$ = 4.2Hz), 24.8, 22.6, 14.24; ESI+: $C_{16}H_{22}F_2O_3Na^+$ {[M+Na]$^+$}, Calc.: 323.1435, Found: 323.1438.

**(±)-1,4-Di(*o*-acetoxyl-benzoylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (283)**



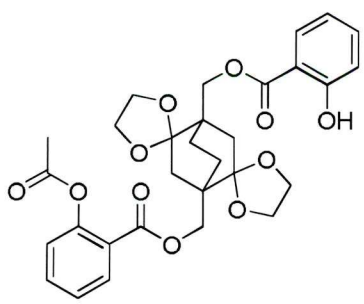
To a 25ml flask fitted with a condenser, acetylsalicylic acid (1.80 g, 10mmol), a drop of pyridine and thionyl chloride (1.1ml, 1.78g, 15mmol) were added in turn. The reaction mixture was stirred and heated at 85°C for 2hrs. Removal of the thionyl chloride residue by rotory evaporation, followed by vacuum drying gave light brown

oil which was used directly without further purification.

To a 50ml flask, pyridine (20ml) and 1,4-di(hydroxylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (4mmol, 1.14g) were added and stirred in a ice-water bath. The crude 2-acetoxylbenzoyl chloride obtained above was diluted with 5ml dichloromethane and transferred to the reaction mixture. Afterwards, the reaction temperature was allowed to rise to room temperature and stirred for a further12hrs. Pure product was obtained by the same work-up procedure as for compound **277** (2.1gram, 86% yield)

$^1$H NMR:δ: 8.02 (dd, *J* = 7.8Hz, *J* = 1.7Hz, 2H), 7.57 (dd, *J* = 15.6Hz, 1.5Hz, 1H), 7.56 (dd, *J* = 2.3Hz, *J* = 0.6Hz, 1H), 7.33 (dd, *J* = 15.6Hz, 1.5Hz, 1H), 7.33 (d, *J* = 1.2Hz, 1H), 7.11 (dd, *J* = 8Hz, 1Hz, 2H), 4.24 (d, *J* = 11Hz, 2H), 4.16 (d, *J* = 11Hz, 2H), 3.88-4.01 (m, 6H), 3.82-3.86 (m, 2H), 2.36 (s, 6H), 2.14 (dd, *J* = 14.2Hz, *J* = 2.7Hz, 2H), 1.84-1.92 (m, 4H), 1.68-1.73 (m, 2H); $^{13}$C NMR: δ:170.2, 164.7, 151.3, 134.3, 132.0, 126.5, 124.2, 123.6, 110.6, 77.6, 66.8, 65.2, 64.9, 42.0, 23.8, 21.5; HRMS, ESI+: $C_{32}H_{34}O_{12}Na$, {$[M+Na]^+$}, Calc.: 633.1948, Found: 633.1928.

**1-(*o*-acetoxyl-benzoylmethyl),4-(*o*-hydroxyl-benzoylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (284)**



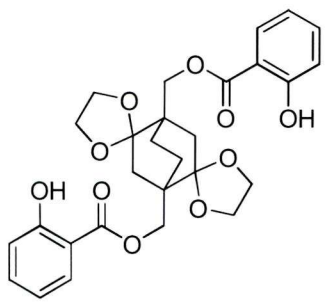

This product was obtained by lipase-hydrolzed resolution reaction. Typically, the reaction was run in organic solvent as followings: To an anhydrous solvent (5ml), di-acetate **283** (60mg, 200 mol), *n*-BuOH (14.8 mg, 18 ml, 400 mol) and 10mg lyophilized enzyme powder were added and stirred at room temperature for a various time.

The reaction was also run in organic solvent-buffer mixed system: for water immiscible solvent, 10mg substrate, 2ml buffer (NaPi, 0.1M, pH 7.0), 2ml organic solvent and 2mg enzyme powder were mixted together and stirred for various times. For water miscible solvents, the reaction solvents ratios were changed to: 4ml buffer and 1ml organic solvent with same amount of substrate and enzyme.

The product was obtained by extraction, evaporation and chromatography (Hexane : EtOAc 1 : 1).

$^1$H NMR:δ: 10.67 (s, 1H), 8.03 (dd, $J$ = 8.0Hz, $J$ = 1.7Hz, 1H), 7.86 (dd, $J$ = 8.0Hz, $J$ = 1.7Hz, 1H), 7.57 (dd, $J$ = 15.5Hz, $J$ = 1.7Hz, 0.5H), 7.57 (dd, $J$ = 1.7Hz, $J$ = 0.6Hz, 0.5H), 7.46 (dd, $J$ = 15.5Hz, $J$ = 1.7Hz, 0.5H), 7.46 (t, $J$ = 15Hz, 0.5H), 7.33 (dd, $J$ = 15.5Hz, $J$ = 1.2Hz, 0.5H), 7.33 (d, $J$ = 1.2Hz, 0.5H), 7.11 (dd, $J$ = 8.0Hz, 1.2Hz, 1H), 6.98 (dd, $J$ = 8.4Hz, $J$ = 0.8Hz, 1H), 6.90 (dd, $J$ = 15.2Hz, $J$ = 1.2Hz, 0.5H), 6.90 (t, $J$ = 1.2Hz, 0.5H), 4.30 (d, $J$ = 11.2Hz, 1H), 4.16 (d, $J$ = 11.2Hz, 1H), 4.25 (d, $J$ = 11Hz, 2H), 3.90-4.05 (m, 6H), 3.81-3.89 (m, 2H), 2.36 (s, 3H), 2.12-2.18 (m, 2H), 2.05 (d, $J$ = 7Hz, 1H), 1.84-1.95 (m, 4H), 1.66-1.78 (m, 2H); $^{13}$C NMR: δ: 170.3, 170.2, 164.7, 161.8, 151.3, 136.1, 134.3, 132.0, 130.4, 126.5, 124.3, 123.6, 119.7, 118.1, 113.1, 110.53, 110.50, 67.1, 66.8, 65.2, 65.1, 64.96, 64.84, 42.1, 42.0, 41.9, 41.8, 23.82, 23.77, 21.5; HRMS, ESI+: $C_{30}H_{32}O_{11}Na$, {$[M+Na]^+$}, Calc.: 591.1842, Found: 591.1837.

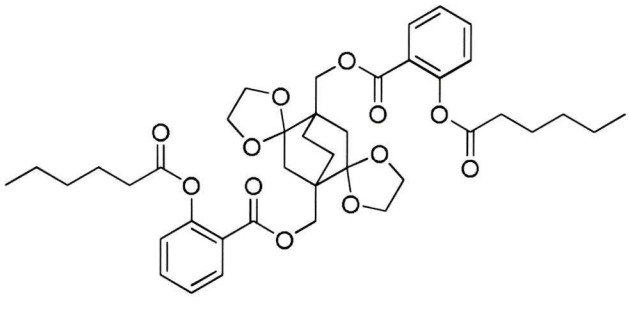
**(±)-1,4-di(*o*-hydroxylbenzoylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane ]} (285)**




This product was obtained by the same reaction described above.

$^1$H NMR:δ: 10.67 (s, 2H), 7.86 (dd, $J$ = 8Hz, $J$ = 1.8Hz, 2H), 7.43-7.50 (m, 2H), 6.97-7.10 (m, 2H), 6.88-6.94 (m, 2H), 4.31 (d, $J$ = 11.1Hz, 2H), 4.25 (d, $J$ = 11.1Hz, 2H), 3.93-4.04 (m, 6H), 3.82-3.90 (m, 2H), 2.17 (dd, $J$ = 14.0Hz, $J$ = 2.6Hz, 2H), 1.88 (d, $J$ = 14Hz, 2H), 1.88-2.00 (m, 2H), 1.68-1.78 (m, 2H); $^{13}$C NMR: δ:170.3, 161.8, 136.1, 130.4, 119.7, 118.1, 113.0, 110.5, 67.0, 65.2, 64.9, 41.9, 23.8; HRMS, ESI+: $C_{28}H_{30}O_{10}Na$, {$[M+Na]^+$}, Calc.: 549.1737, Found: 549.1745.

**(±)-1,4-di(*o*-hexanoyloxybenzoylmethyl)-bicyclo[2.2.2]octan-2,5-di-{2'-[1,3-dioxolane]} (286)**

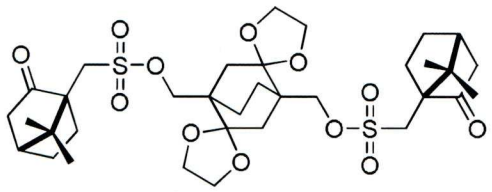


Compound **285** (105mg, 0.4mmol) and triethyl amine (120mg, 165 L, 1.2mmol) were dissolved in diethyl ether (5ml). To this resulting mixture hexanoyl chloride (134mg, 140 μL and 1.0mmol) was added at room temperature and stirred for 3hrs. The reaction mixture was diluted with diethyl ether (20ml) and washed with 5% HCl aqueous solution, saturated $NaHCO_3$ solution and brine respectively. The organic layer was collected and dried on anhydrous $MgSO_4$. Removal of solid and solvent followed by flash column gave product **286** as a sticky oil (280mg, 97% yield)

$^1$H NMR:δ: 7.93 (dd, $J$ = 7.8Hz, $J$ = 1.7Hz, 2H); 7.48 (td, $J$ = 7.8Hz, 1.7Hz, 2H); 7.24 (td; $J$ = 7.8Hz, $J$ = 1.0Hz, 2H); 7.01 (dd, $J$ = 7.8Hz, 1.0Hz, 2H); 4.16 (d, $J$ = 11Hz, 2H); 4.07 (d, $J$ = 11Hz, 2H); 3.72-3.94 (m, 8H), 2.56 (t, $J$ = 7.5Hz, 4H); 2.05 (dd, $J$ = 14Hz, $J$ = 2.4Hz, 2H); 1.80 (d, $J$ = 14Hz, 2H), 1.55-1.82 (m, 8H), 1.3-1.35 (m, 8H), 0.86 (t, $J$ = 7.0Hz, 6H); $^{13}$C NMR: δ:171.4, 163.2, 149.9, 132.7, 130.5, 124.9, 122.8, 122.4, 109.1, 65.3, 63.7, 63.5, 40.6, 31.2, 30.3, 23.2, 22.4, 21.3, 12.9; HRMS, ESI+:

$C_{40}H_{50}O_{12}Na$, {$[M+Na]^+$}, Calc.: 745.3200, Found: 745.3187.

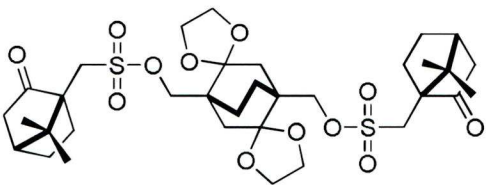
**([1(*RS*),1(*RS*),1'*S*,1'*S*]-1,4-di(camphorsulphonyloxymethyl)-bicyclo[2.2.2]octan-2, 5-di-{2'-[1,3-dioxolane]} (288)**



This compound was made according to the same procedure as for **264** (286 mg starting material gave 712 mg product, 99% yield).

$^1$H NMR:δ: 4.10-4.23 (m, 4H), 3.90-4.00 (m, 6H), 3.81-3.86 (m, 2H), 3.58 (dd, $J$ = 15Hz, $J$ = 4.0Hz, 2H), 2.98 (dd, $J$ = 15Hz, $J$ = 1.7Hz, 2H), 2.45-2.53 (m, 2H), 2.39 (dt, $J$ = 18.6Hz, $J$ = 4Hz, 2H), 2.00-2.14 (m, 6H), 1.96 (d, $J$ = 18.5Hz, 2H), 1.89 (dd, $J$ = 14Hz, $J$ = 4.0Hz, 2H), 1.74-1.80 (m, 2H), 1.60-1.69 (m, 4H), 1.40-1.48 (m, 2H), 1.13 (s, 6H), 0.88 (d, $J$ = 1Hz, 6H); $^{13}$C NMR: δ:214.90, 214.84, 110.12, 110.10, 77.11, 72.14, 72.07, 64.99, 64.69, 64.67, 58.36, 48.34, 48.32, 47.08, 47.01, 43.19, 43.17, 42.90, 41.94, 40.91, 27.28, 25.36, 25.30, 23.22, 20.27, 20.11; HRMS, ESI+: $C_{34}H_{50}O_{12}S_2Na$, {$[M+Na]^+$}, Calc.: 737.2641, Found: 737.2634.

**(1*S*,1*S*,1'*S*,1'*S*)-1,4-di(camphorsulphonyloxymethyl)-Bicyclo[2.2.2]octan-2,5-di-{2 '-[1,3-dioxolane]} (288)**

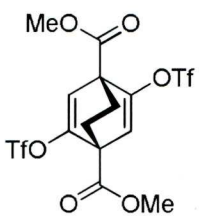


This compound was made according to the same procedure as for **264** (28 mg starting material gave 71 mg product, 99% yield).

$^1$H NMR:δ: 4.22(d, $J$ = 9.5Hz, 2H), 4.13(d, $J$ = 9.5Hz, 2H), 3.90-3.98 (m, 6H),

3.80-3.86 (m, 2H), 3.57 (d, $J$ = 15Hz, 2H), 2.98 (d, $J$ = 15Hz, 2H), 2.45- 2.52 (m, 2H), 2.40 (dt, $J$ = 18.5Hz, $J$ = 4.0Hz, 2H), 2.13 (t, $J$ = 4.4Hz, 2H), 1.99-2.10 (m, 4H), 1.95 (d, $J$ = 18.5Hz, 2H), 1.88 (d, $J$ = 15Hz, 2H), 1.74-1.82 (m, 2H), 1.61-1.71 (m, 6H), 1.41-1.48 (m, 2H), 1.12 (s, 6H), 0.89 (s, 6H); $^{13}$C NMR: δ: 214.8, 110.1, 72.1, 65.0, 64.7, 58.4, 48.3, 47.1, 43.2, 42.9, 41.9, 40.9, 27.3, 25.4, 23.2, 20.3, 20.1; HRMS, ESI+: $C_{34}H_{50}O_{12}S_2Na$, {$[M+Na]^+$}, Calc.: 737.2641, Found: 737.2652.

**(*S*,*S*)-1,4-di(methoxycarbonyl)-2,5-di(trifluromethysulfonyloxy)bicyclo[2.2.2]octa n-2, 5-diene (295)**

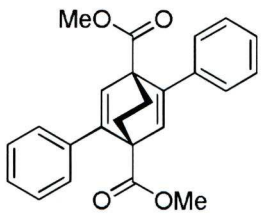



Diketone (*S*,*S*)-**254** (254 mg, 1 mmol) was added to a 25 mL flask containing anhydrous THF (5 mL). The solution was stirred, cooled to -78°C and LHMDS (2.2, mL, 1.06M, 2.33 mmol) was added. The reaction mixture was stirred for 30 min and triflic anhydride (648 mg, 2.3mmol) was added in one portion. The reaction finished instantaneously and was quenched with saturated $NaHCO_3$ aqueous solution (10 mL) then transferred to a separating funnel. The mixture was extracted with EtOAc (3 × 15 mL), extracts were combined and washed with water and brine then dried over $Na_2SO_4$. After filtration and evaporation the crude product was purified by flash column chromatography (Hexane:EtOAc; 9:1) to give pure product (*S,S*)-**295** (362 mg, 70% yield) as colorless oil.

$^1$H NMR δ 6.62 (s, 2H), 3.92 (s, 6H), 2.32-2.38 (m, 2H), 1.90-1.97 (m, 2H); $^{13}$C NMR δ 168.1, 152.2, 121.0, 118.7 (q, $J$ = 320Hz), 54.9, 53.8, 31.0.

HRMS ESI+: $C_{14}H_{12}F_6O_{10}S_2Na^+$ {$[M+Na]^+$}, Calc.: 540.9674, Found: 540.9695.

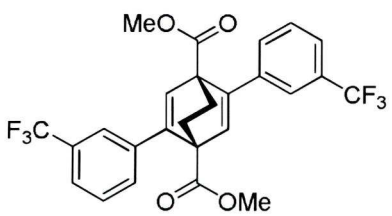
**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (296a)**




(*S,S*)-bis enol triflate (570 mg, 1.1 mmol) was dissolved in toluene (20 mL) and EtOH (7mL) in a 100 ml flask. To this solution, phenylboronic acid (360 mg, 3.0mmol), of $Na_2CO_3$ aqueous solution (4.5 mL, 2.0M, 9mmol) and tetrakis-(triphenylphosphine)palladium (63mg, 55 μmol, 5 mol%) were added in turn. The resulting mixture was degassed, charged with nitrogen and then stirred at room temperature for 6h for full conversion. The reaction mixture was extracted with $Et_2O$ (20 mL) and washed with water and brine. After being dried over $Na_2SO_4$, the organic solution was filtered and evaporation of the solvents gave crude product which was purified by flash column chromatography (hexane:EtOAc; 5:1) to give pure product (*S,S*)-(+)-**296a** as white solid (390 mg, 95%).

$^1$H NMR δ 7.25-7.32(m, 6H), 7.15-7.17(m, 4H), 6.64 (s, 2H), 3.51 (s, 6H), 2.12-2.18 (m, 2H), 1.87-1.92 (m, 2H), $^{13}$C NMR δ 174.4, 148.0, 138.4, 131.9, 128.5, 127.7, 126.9, 57.4, 52.3, 30.6, HRMS ESI+: $C_{24}H_{22}O_4Na^+$ {$[M+Na]^+$}, Calc.: 397.1416, Found: 397.1418; $[\alpha]_D^{20}$ = +60.8 (*c* 0.44, $CHCl_3$).

**(*S,S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di(3'-trifluoromethylphenyl)bicyclo[2.2.2] octan-2,5-diene (296b)**

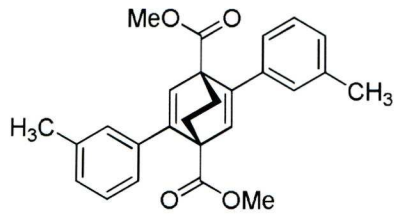



This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give (*S,S*)-(+)-**296b** as a white solid (125mg of **254** gave 143 mg of **296b**, 56% overall yield for 2 steps).

$^1$H NMR δ 7.54 (d, *J* = 7.6Hz, 2H), 7.43 (t, *J* = 7.6Hz, 4H), 7.35 (d, *J* = 7.6Hz, 2H), 6.76 (s, 2H), 3.55 (s, 6H), 2.16-2.22 (m, 2H), 1.90-1.98 (m, 2H); $^{13}$C NMR δ 172.3,

145.5, 137.4, 131.8, 129.6 (q, $J$ = 32.0Hz), 129.0, 127.7, 123.2 (q, $J$ = 3.4Hz), 123.0 (q, $J$ = 271Hz), 122.4 (q, $J$ = 3.8Hz), 56.0, 51.1, 29.2; HRMS ESI+: $C_{26}H_{20}O_4F_6Na^+$ {$[M+Na]^+$}, Calc.: 533.1163, Found: 533.1154; $[\alpha]_D^{20}$ = +40.0 (*c* 0.90, $CHCl_3$).

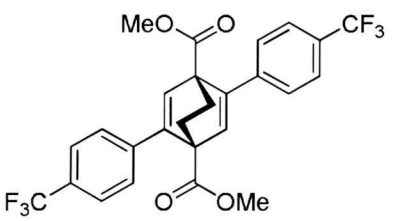
**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di(3'-methylphenyl)bicyclo[2.2.2] octan-2,5-diene (296c)**




This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give (*S,S*)-(+)-**296c** as a white solid (125mg of **254** gave 137 mg of **296c**, 68% overall yield for 2 steps).

$^1$H NMR δ 7.17 (t, $J$ = 7.6Hz, 2H), 7.05 (d, $J$ = 7.6Hz, 2H), 6.94-6.98 (m, 4H), 6.62 (s, 2H), 3.52 (s, 6H), 2.32 (s, 6H), 2.11-2.17 (m, 2H), 1.86-1.93 (m, 2H); $^{13}$C NMR δ 174.6, 148.1, 138.4, 138.2, 131.7, 128.5, 128.4, 123.8, 57.4, 52.3, 30.7, 21.8; HRMS ESI+: $C_{26}H_{26}O_4Na^+$ {$[M+Na]^+$}, Calc.: 425.1729, Found: 425.1716; $[\alpha]_D^{20}$ = +51.5 (*c* 0.42, $CHCl_3$).

**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di(4'-trifluoromethylphenyl)bicyclo[2.2.2] octan-2,5-diene (296d)**

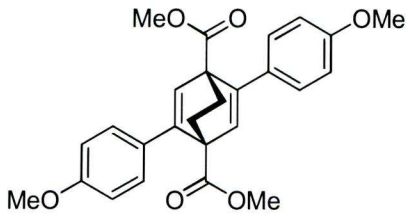



This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give (*S,S*)-(+)-**296d** as a white solid (125mg of **254** gave 163 mg of **296d** 64% overall yield for 2 steps).

$^1$H NMR δ 7.56 (d, $J$ = 10.2Hz, 4H), 6.82 (d, $J$ =10.2Hz, 4H), 6.74 (s, 2H), 3.54 (s, 6H), 2.14-2.20 (m, 2H), 1.90-1.96(m, 2H); $^{13}$C NMR δ 173.73, 147.0, 141.8, 133.5,

130.0 ( q, 32.4Hz), 127.3, 125.5 (q, $J$ = 3.4Hz), 124.5 (q, $J$ = 270Hz), 57.4, 52.6, 30.6; HRMS ESI+: $C_{26}H_{20}O_4F_6Na^+$ {[M+Na]$^+$}, Calc.: 533.1163, Found: 533.1167; $[\alpha]_D^{20}$ = +41.6 ($c$ 0.30, $CHCl_3$).

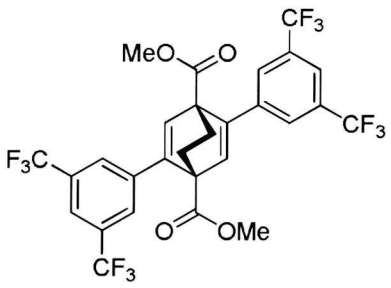
**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di(4'-methoxylphenyl)bicyclo[2.2.2] octan-2,5-diene (296e)**




This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give (*S,S*)-(+)-**296e** as a white solid (300mg **254** gave 338 mg **296e**, 66% overall yield for 2 steps).

$^1$H NMR δ 7.08 (d, $J$ = 8.7Hz, 4H), 6.82 (d, $J$ = 8.7Hz, 4H), 6.56 (s, 2H), 3.80 (s, 6H), 3.54 (s, 6H), 2.07-2.14 (m, 2H), 1.83-1.90(m, 2H); $^{13}$C NMR δ 174.6, 159.3, 147.6, 131.0, 128.2, 113.9, 57.4, 55.6, 52.4, 30.7; HRMS ESI+: $C_{26}H_{26}O_6Na^+$ {[M+Na]$^+$}, Calc.: 457.1627, Found: 457.1617; $[\alpha]_D^{20}$ = +68.0 ($c$ 0.31, $CHCl_3$).

**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di{3',5'-di(trifluromethyl)phenyl}bicyclo[2.2.2] octan-2,5-diene (296f)**

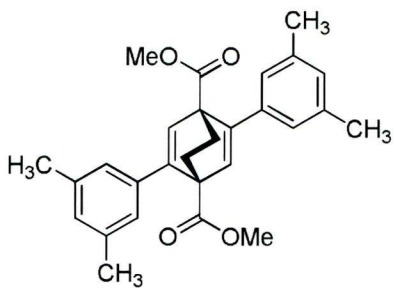



This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give pure product (*S,S*)-(+)-**296f** as a white solid (190mg of **254** gave 320 mg of **296f**, 66% overall yield for 2 steps).

$^1$H NMR δ 7.81 (s, 2H), 7.62 (s, 4H), 6.89 (s, 2H), 3.61 (s, 6H), 2.19-2.25 (m, 2H),

1.94-2.01 (m, 2H), $^{13}$C NMR δ 172.9, 145.8, 139.8, 134.8, 132.1 (q, $J$ = 33Hz), 127.3, 123.5 (q, $J$ = 271Hz), 121.7 (q, $J$ = 3.8Hz), 57.3, 52.8, 30.6; HRMS ESI+: $C_{28}H_{18}F_{12}O_4Na^+$ {[M+Na]$^+$}, Calc.: 669.0911, Found: 669.0931; $[\alpha]_D^{20}$ = +39.6 (*c* 0.55, $CHCl_3$)

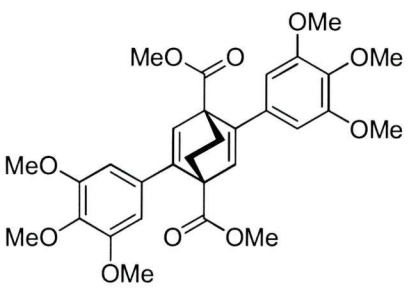
**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di{3',5'-di(trifluromethyl)phenyl}bicyclo[2.2.2] octan-2,5-diene (296g)**




This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give pure product (*S,S*)-(+)-**296g** as a white solid (125mg of **254** gave 140 mg of **296g**, 65% overall yield for 2 steps).

$^1$H NMR δ 6.81 (s, 2H), 7.71 (s, 4H), 6.52 (s, 2H), 3.47 (s, 6H), 2.21 (s, 12H), 2.00 -2.10 (m, 2H), 1.75 – 1.85 (m, 2H), $^{13}$C NMR δ 173.2, 146.7, 136.9, 136.5, 130.1, 127.9, 123.2, 55.9, 50.9, 29.2, 20.2; HRMS ESI+: $C_{28}H_{30}O_4Na^+$ {[M+Na]$^+$}, Calc.: 453.2042, Found: 453.2048; $[\alpha]_D^{20}$ = +43.0 (*c* 0.56, $CHCl_3$)

**(*S*,*S*)-(+)-1,4-di(methoxycarbonyl)-2,5-di{3',4',5'-tri(methoxyl)phenyl}bicyclo [2.2.2]octan -2,5-diene (296h)**

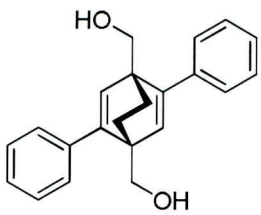



This compound was made according to the procedure for compound (*S,S*)-(+)-**296a** above to give pure product (*S,S*)-(+)-**296h** as a white solid (152mg of **254** gave 200

mg of **296h**, 60% overall yield for 2 steps).

$^1$H NMR δ 6.64 (s, 2H), 6.39 (s, 4H), 3.85 (s, 12H), 3.84 (s, 6H), 3.58 (s, 6H), 2.13-2.18 (m, 2H), 1.88-1.94 (m, 2H); $^{13}$C NMR δ 174.6, 153.4, 148.0, 137.7, 133.9, 131.5, 103.9, 61.3, 57.5, 56.5, 52.6, 30.8; HRMS ESI+: $C_{30}H_{34}O_{10}Na^+$ {[M+Na]$^+$}, Calc.: 577.2050, Found: 577.2048; $[\alpha]_D^{20}$ = +36 (*c* 0.37, $CHCl_3$)

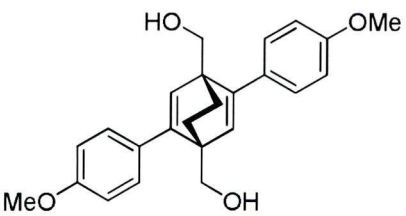
**(*S*,*S*)-(+)-1,4-di(hydroxylmethyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (297a)**




The (*S*,*S*)-(+)-**296a** (171mg, 0.45 mmol) was dissolved in THF (5 mL) and $Et_2O$ (5 mL). To this solution $LiAlH_4$ (38 mg, 1 mmol) was added under nitrogen. The reaction finished in 5 min after the addition of $LiAlH_4$. The reaction was worked up as described for compound **256** to give pure product as sticky oil (145 mg, 99%).

$^1$H NMR δ 7.20-7.40 (m, 10H), 6.27 (s, 2H), 4.15 (dd, *J* = 11.5Hz, *J* = 6Hz, 2H), 4.00 (dd, *J* = 11.5, *J* = 7Hz, 2H), 1.70-1.77 (m, 2H), 1.58-1.65 (m, 2H), 1.17-1.26 (m, 2H, -OH); $^{13}$C NMR δ 149.6, 139.6, 136.0, 128.8, 128.1, 127.6, 65.8, 52.1, 31.0; HRMS ESI+: $C_{22}H_{22}O_2Na^+$ {[M+Na]$^+$}, Calc.: 341.1517, Found: 341.1513; $[\alpha]_D^{20}$ = +44.4 (*c* 0.53, $CHCl_3$)

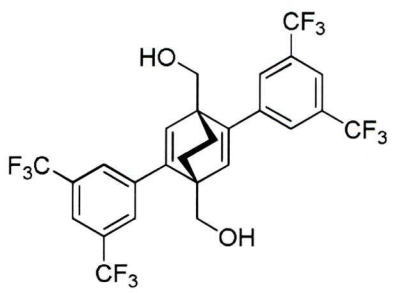
**(*S*,*S*)-1,4-di(hydroxymethyl)-2,5-di(4'-dimethoxylphenyl)bicyclo[2.2.2] octan-2,5-diene (297e)**




This compound was made using the same procedure as used for (*S*,*S*)-(+)-**297a**. 220 mg starting material gave 182mg product (*S*,*S*)-(+)-**297e** (96%).

$^1$H NMR δ 7.15(d, *J* = 8.6Hz, 4H), 6.87 (d, *J* = 8.6Hz, 4H), 6.20 (s, 2H), 4.12 (d, *J* = 11.5Hz, 2H), 3.99 (d, *J* = 11.5Hz, 2H), 3.81 (s, 6H), 1.66-1.73 (m, 2H), 1.53-1.60(m, 2H), 1.23(brs, 2H); $^{13}$C NMR δ 159.2, 149.1, 135.6, 131.9, 129.2, 114.3, 65.9, 55.7, 52.1, 31.0; HRMS ESI+: $C_{24}H_{26}O_4Na^+$ {[M+Na]$^+$}, Calc.: 401.1729, Found: 425.1709; $[\alpha]_D^{20}$ = +62.8 (*c* 0.30, $CHCl_3$).

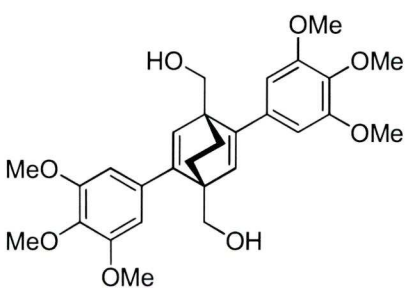
**(*S*,*S*)-(+)-1,4-di(Hydoxymethyl)-2,5-di{3',5'-di(trifluromethyl)phenyl}bicyclo [2.2.2]octan -2,5-diene (297f)**




This compound was made using the same procedure as used for (*S,S*)-(+)-**297a**. 200 mg starting material gave product (*S,S*)-(+)-**297f** (180mg 99%).

$^1$H NMR δ 7.73 (s, 2H), 7.65 (s, 4H), 6.39 (s, 2H), 4.03 (d, *J* = 10.8Hz, 2H), 3.93 (d, *J* = 10.8Hz, 2H), 1.65 (s, 4H), 1.51 (brs., 2H); $^{13}$C NMR δ 146.4, 139.9, 136.6, 130.3 (q, *J* = 33Hz), 127.2, 122.2 (q, *J* = 271Hz), 119.9 (hept. *J* value can not be determined) 63.4, 50.4, 29.2; HRMS ESI- : $C_{28}H_{17}F_{12}O_2^-$ {[M-H]$^-$} Calc. 589.1037, Found: 589.1008; $[\alpha]_D^{20}$ = +43.2 (*c* 0.49, $CHCl_3$)

**(*S*,*S*)-1,4-di(Hydoxymethyl)-2,5-di{3',4',5'-tri(methoxyl)phenyl}bicyclo [2.2.2]octan -2,5-diene (297h)**

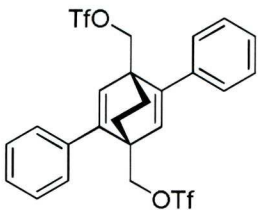



This compound was made using the same procedure as used for (*S,S*)-(+)-**297a**. 150

mg starting material gave product (*S,S*)-(+)-**297h** (134mg 99%).

$^1$H NMR δ 6.43 (s, 4H), 6.29 (s, 2H), 4.19 (d, *J* = 11.6Hz, 2H), 4.03 (d, *J* = 11.6Hz, 2H), 3.87 (s, 12H), 3.86 (s, 6H), 1.63-1.75 (m, 2H), 1.56-1.62(m, 2H), 1.39 (brs, 2H); $^{13}$C NMR δ 153.5, 149.5, 137.7, 135.8, 135.0, 105.1, 66.9, 61.3, 56.6, 52.2, 31.1; HRMS ESI+: $C_{28}H_{34}O_8Na^+$ {$[M+Na]^+$}, Calc.: 521.2151, Found: 521.2160.

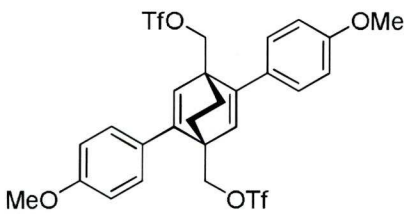
**(*S,S*)-1,4-di(trifluoromethanesulfonyloxy)-2,5-diphenylbicyclo[2.2.2]octan-2, 5-diene (298a)**




572mg of the diol (*S,S*)-**297a** was bis triflated according to the procedure used for **265** to give product (*S,S*)- **298a** (1.02 g, 99%).

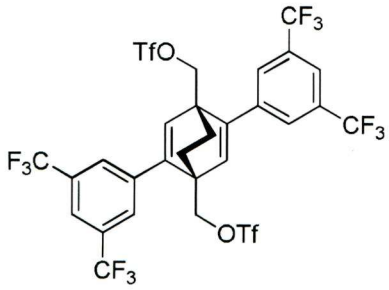
$^1$H NMR δ 7.32-7.40 (m, 6H), 7.10-7.12 (m, 4H), 6.24 (s, 2H), 4.89 (d, *J* = 10Hz, 2H), 4.73 (d, *J* = 10Hz, 2H), 1.74-1.90 (m, 4H); $^{13}$C NMR δ 149.1, 136.9, 128.9, 128.4, 128.2, 78.3, 49.1, 30.6; HRMS ESI+: $C_{24}H_{20}F_6O_6S_2Na^+$, {$[M+Na]^+$}, Calc.: 605.0503, Found: 605.0530. (Due to the unstability of this compound the $[\alpha]_D$ value was not measured.)

**(*S,S*)-1,4-di(trifluoromethanesulfonyloxy)-2,5-di(4'-dimethoxylphenyl)bicyclo[2.2 .2] octan-2,5-diene (298e)**




The triflate derivative was made using the same procedures as described for compound **298a**. The resulting bistriflate was unstable and used without characterization for the subsequent reaction.

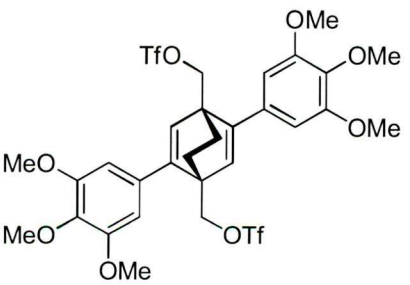
**(*S*,*S*)-1,4-di(trifluoromethanesulfonyloxy)-2,5-di{3',5'-di(trifluromethyl)phenyl}bicyclo [2.2.2]octan -2,5-diene (298f)**




This compound was made using the same procedure as used for **297a**. 150mg starting material **297f** gave 182 mg product (*S,S*)-**298f** (84% overall yield).

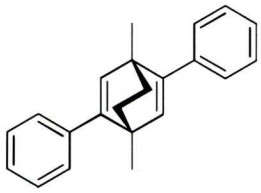
$^{1}$H NMR δ 7.92 (s, 2H), 7.60 (s, 4H), 6.40 (s, 2H), 4.80 (s, 4H), 1.83-1.97 (m, 4H); $^{13}$C NMR δ 146.9, 138.7, 135.5, 132.7 (q, $J$ = 134Hz) 128.5, 76.2, 49.7, 30.5. (Not all $J_{C\text{-}F}$ coupling data were observed due to the low concentration. Due to the unstability of this compound the $[\alpha]_D$ value was not measured.)

**(*S*,*S*)-1,4-di(trifluoromethanesulfonyloxy)-2,5-di{3',4',5'-tri(methoxyl)phenyl}bicyclo [2.2.2]octan -2,5-diene (298h)**




The triflate derivative was made using the same procedures as described for compound **298a**. The resulting bistriflate was unstable and used without characterization for the subsequent reaction

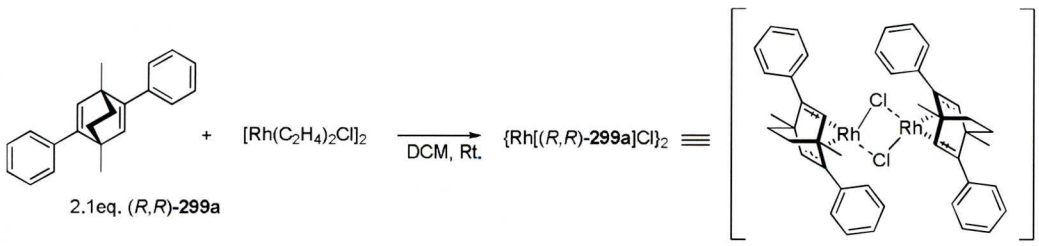
**(*R*,*R*)-(+)1,4-dimethyl-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (299a)**



The bis triflate (*S,S*)- **298a** (582 mg, 1.0 mmol) was dissolved in anhydrous THF (20ml) and cooled to -78°C. To this a stirred solution $LiHBEt_3$ (5 mL, 5.0mmol) was added in one portion and the reaction mixture allowed to warm to room temperature. The reaction was stirred for a further 30min and around 10 g of silica gel was added which was pre-cooled in an ice-water bath. Removal of the solvent gave a silica gel powder with product absorbed, which was loaded onto a short silica column and washed with pure hexane to give pure product (*R,R*)- **299a** as colorless oil (370 mg, 99%).

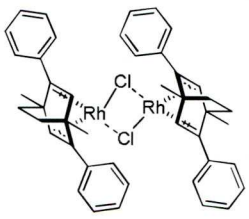
$^1H$ NMR δ 7.13-7.32 (m, 10H), 5.97 (s, 2H), 1.58-1.66 (m, 2H), 1.46-1.54 (m, 2H), 1.42 (s, 6H); $^{13}C$ NMR δ 151.6, 140.2, 139.0, 128.7, 128.1, 126.8, 45.2, 37.5, 22.6; HRMS: $C_{22}H_{23}$, {$[M+H]^+$}Calc.: 287.1794, Found: 287.1794; $[\alpha]_D^{20}$ = +127.2 (*c* 0.46, $CHCl_3$).

**Synthesis of {Rh[(*R,R*)-299a]Cl}$_2$ and X-ray single crystal structure.**




**{[(*R,R*)-(+)1,4-dimethyl-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene]-RhCl}$_2$**

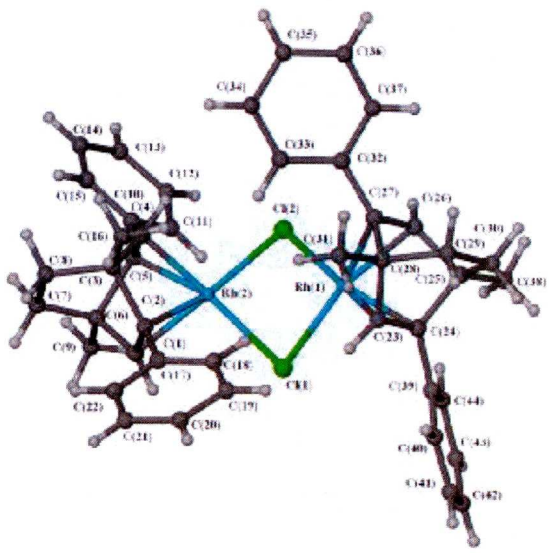
**{Rh[(*R,R*)-299a]Cl}$_2$**




To a 10ml flask, chiral diene ligand (*R,R*)-**299a** (30 mg, 0.105 mmol), $[Rh(C_2H_4)_2Cl]_2$

(19.4mg, 0.100mmol) and dichloromethane (1 mL) was added, and the resulting mixture was stirred for 2hrs at room temperature. Removal of the solvents and purification by flash column chromatography gave the product as an orange solid (42 mg, 92%). A single crystal was obtained by recrystallization from dichloromethane-Hexane.

$^1$H NMR δ 7.87 (d, $J$ = 6.4 Hz, 4H), 7.19-7.25 (m, 6H), 3.34 (s, 2H), 1.78 (s, 6H), 1.14-1.21 (m, 2H), 1.03-1.11 (m, 2H); $^{13}$C NMR δ 138.2, 131.3, 127.5, 127.4, 49.9 (d, $J$ = 11.4 Hz), 56.1 (d, $J$ = 10.2 Hz), 49.9 (d, $J$ = 3.8 Hz), 36.2, 22.4. $[\alpha]_D^{20}$ = +64.0 (*c* 0.50, $CHCl_3$).

| ***Crystal Data*** | |
|---|---|
| $C_{44}H_{44}Cl_2Rh_2$<br>$M$ = 849.51<br>red-orange thin prism<br>0.32 0.17 0.03 mm$^3$<br>monoclinic, space group $P2_1$ (No. 4)<br>$a$ = 11.929(4) Å<br>$b$ = 22.192(8) Å<br>$c$ = 13.995(5) Å<br>= 90.216(4)°<br>$V$ = 3705(2) Å$^3$<br>$Z$ = 4<br>$D_c$ = 1.523 g/cm$^3$<br>$T$ = 100(2)K<br>18472 reflections collected, 9571 unique $R_{int}$ = 0.0746<br>Final *GooF* = 1.033<br>*R1* = 0.0639<br>*wR2* = 0.1284<br>= 1.066 mm$^{-1}$<br>Flack parameter = 0.02(6) |  |

**Data collection, structure solution and refinement**

A crystal was selected from a sample submitted by Yunfei Luo from the research group of Dr. Andrew Carnell. The crystals were very thin needles and plates with twinning and defect structures. A crystal with good morphology, though obviously a twin was selected from the sample and mounted on a glass fibre and placed in a cold stream at 100K. Single crystal X-ray data were collected at 100K on a Bruker D8 diffractometer with an APEX CCD detector, and 1.5 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Exposure times of 20 s per frame and scan widths of 0.3° were used throughout the data collection. Two 180° $\omega$ scans provided data with an average completeness of 99.9% in the $\theta$ range 1.9 to 23.25°. The frames were integrated with the SAINT v6.45a (Bruker, 2005).[6] Since the crystal was a very thin plate and twinned, a numerical absorption based on face-indexing was carried out using the program SADABS V2008-1[7] rather than a correction based on multiply measured equivalent reflections.

**Structure solution and refinement.**

The structure was solved by direct methods in the space group $P2_1$ using the program SHELXS (Sheldrick, 2008).[8] The initial structure solution contained 2 complete $C_{44}H_{44}Cl_2Rh_2$ molecules. Although these molecules were structurally very similar, no additional crystallographic symmetry was present between the molecules, *i.e.* there are two independent $Rh_2$ molecules, and 8 $C_{44}H_{44}Cl_2Rh_2$ molecules per unit cell. The data were twinned and the structure was refined with the twin law: 2-fold rotation about cell axis *a*. The fraction of the smaller component of the twin refined to 0.23. Due to the strong absorption and the twinning the crystal faces were indexed and a numerical absorption correction was applied.
The structure is chiral, both molecules are chiral with the same handedness, and the absolute structure confirmed by the refined Flack parameter.

Table 1. Crystal data and structure refinement for YL02100m.

| | |
|---|---|
| Identification code | yl02100m |
| Empirical formula | C44 H44 Cl2 Rh2 |

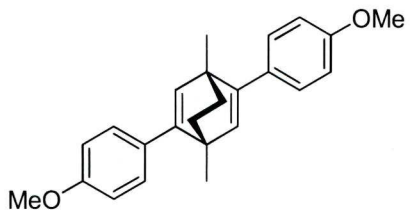
[6] Bruker (2005), SAINT V6.45a, Bruker AXS Inc., Madison, WI, USA.

[7] Bruker (2008), SADABS V2008-1, Bruker AXS Inc., Madison, WI, USA.

[8] Sheldrick, G.M. (2008), ***Acta Cryst.*** A64, 112-122.

| | | |
|---|---|---|
| Formula weight | 849.51 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P21 | |
| Unit cell dimensions | a = 11.929(4) Å | = 90°. |
| | b = 22.192(8) Å | = 90.216(4)°. |
| | c = 13.995(5) Å | = 90°. |
| Volume | 3705(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.523 $Mg/m^3$ | |
| Absorption coefficient | 1.066 $mm^{-1}$ | |
| F(000) | 1728 | |
| Crystal size | 0.32 x 0.17 x 0.03 $mm^3$ | |
| Theta range for data collection | 1.46 to 23.25°. | |
| Index ranges | -13<=h<=12, -24<=k<=24, -15<=l<=15 | |
| Reflections collected | 18472 | |
| Independent reflections | 9571 [R(int) = 0.0746] | |
| Completeness to theta = 23.25° | 99.9 % | |
| Absorption correction | Numerical | |
| Max. and min. transmission | 0.9687 and 0.7267 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 9571 / 1819 / 844 | |
| Goodness-of-fit on $F^2$ | 1.033 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0639, wR2 = 0.1284 | |
| R indices (all data) | R1 = 0.0846, wR2 = 0.1382 | |
| Absolute structure parameter | 0.02(6) | |
| Largest diff. peak and hole | 1.155 and -1.081 $e.Å^{-3}$ | |

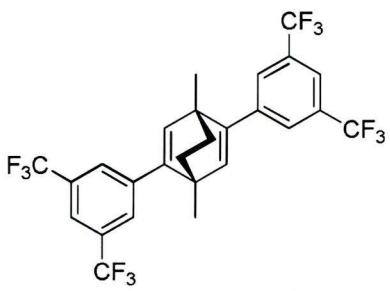
**(*R,R*)-(+)1,4-dimethyl-2,5-di[4'-(methoxyl)phenyl]bicyclo[2.2.2]octan-2,5-diene (299e)**




This compound was made using the same procedure as used for (*R,R*)-**299a**. (The bis triflate starting material for this compound was unstable, especially in chloroform. It was therefore subjected to reduction directly immediately after it was isolated. 90 mg starting material (*S,S*)-**297e** gave product (*R,R*)-**299e** (76 mg 93%).

$^1$H NMR δ 7.07 (d, *J* = 8.6Hz, 4H), 6.87 (d, *J* = 8.6Hz, 4H), 5.91 (s, 2H), 3.81 (s, 6H), 1.54-1.61 (m, 2H), 1.43-1.50(m, 2H), 1.40(s, 6H); $^{13}$C NMR δ 158.7, 151.1, 138.4, 132.6, 129.8, 113.5, 55.6, 45.2, 37.6, 22.7; HRMS ESI+: $C_{24}H_{27}O_2^+$ {$[M+H]^+$}, Calc.: 347.2011, Found: 347.1995; $[\alpha]_D^{20}$ =+47.3 (*c* 0.29, $CHCl_3$).

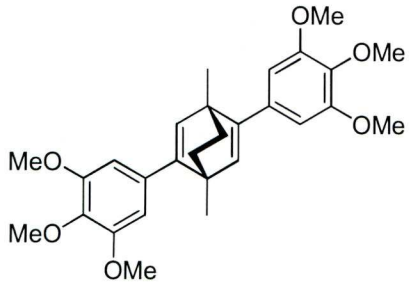
**(*R,R*)-(+)-1,4-Dimethyl-2,5-{3',5'-di(trifluromethyl)phenyl}[2.2.2]octan-2,5-diene (299f)**




This compound was made using the same procedure as used for (*R,R*)-**299a**. 160 mg of (*S,S*)- **298f** gave 100 mg (96% yield) pure product (*R,R*)- (*R,R*)-**299f** as white solid.

$^1$H NMR δ 7.72 (s, 2H), 7.51 (s, 4H), 6.07 (s, 2H), 1.48-1.66 (m, 4H), 1.38 (s, 6H); $^{13}$C NMR δ 147.9, 140.1, 139.9, 130.2 (q, *J* = 33Hz), 127.2, 122.3 (q, *J* = 271Hz), 119.6 (q, *J* = 3.8Hz), 43.9, 35.8, 20.8; Elemental analysis: $C_{26}H_{18}F_{12}$, Calc.: C 55.92, H 3.25, Found: C55.8, H 3.23; MS CI: $M^+$ 558; $[\alpha]_D^{20}$ = +61.1 (*c* 0.43, $CHCl_3$).

**(*R*,*R*)-(+)-1,4-di(Hydoxymethyl)-2,5-di{3',4',5'-tri(methoxyl)phenyl}bicyclo [2.2.2]octan -2,5-diene (299h)**



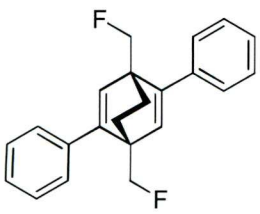

This compound was made using the same procedure as used for (*R,R*)-**299a**. 75 mg of (*S,S*)- **297h** gave 66 mg (94% yield) pure product (*R,R*)-**299h** as white solid.

$^1$H NMR δ 6.34 (s, 4H), 5.99 (s, 2H), 3.87 (s, 12H), 3.86 (s, 6H), 1.59-1.65 (m, 2H), 1.49-1.54 (m, 2H), 1.47 (s, 6H);

$^{13}$C NMR δ 152.9, 151.6, 138.6, 137.2, 135.6, 105.8, 61.3, 56.5, 45.3, 37.6, 22.7;

$[\alpha]_D^{20}$ = +95.5 (*c* 0.69, $CHCl_3$)

**(*S*,*S*)-(+)-1,4-di(fluoromethyl)-2,5-diphenylbicyclo[2.2.2]octan-2,5-diene (291)**



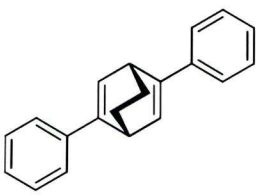

The (*S,S*)-**298** (50 mg, 86μmol) was dissolved in anhydrous THF (5ml) and stirred at room temperature. To this solution TBAF (tetra-*n*butylammonium fluoride THF solution, 0.43 mL, 430μmol) was added in one portion and the reaction mixture allowed to warm 40°C for 3hrs. To this reaction mixture ca. 2g of silica gel was added and resultant mixture was subjected to rotary evaporation to remove all solvent to give silica powder with product absorbed. This was loaded onto a short silica pad and washed with pure hexane to give pure product (*S,S*)-(+)-**291** (26mgs, 95% yield).

$^1$H NMR δ 7.17-7.35 (m, 10H), 6.30 (s, 2H), 4.62-4.91 (doublet of a AB quartets, $J_{H\text{-}F}$ = 47Hz, *J* = 9.5Hz, 4H), 1.63-1.78 (m, 4H); $^{13}$C NMR δ 149.3, 138.5, 134.0 (d, *J* = 26Hz), 138.5, 127.7, 85.8 (d, *J* = 678Hz), 50.3 (d, *J* = 73Hz), 29.9 (d, *J* = 23Hz);

HRMS EI: $C_{22}H_{21}F_2$ {$[M+H]^+$}, Calc. 323.1606, Found: 323.1601; $[\alpha]_D^{20}$ = +125.9 (*c* 0.37, $CHCl_3$)

### 5.2.3 Synthesis of chiral ligands based on bicyclo[2.2.2]octan -2,5-done

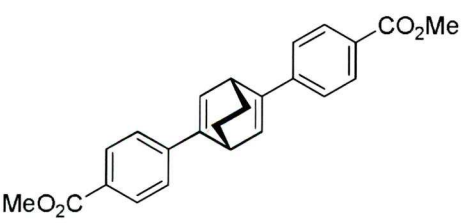
#### (*R*,*R*)-(+)-2,5-di(phenyl)bicyclo [2.2.2]octan -2,5-diene (27a)



This compound was prepared according to ref. [101] from (*R*,*R*)-(-)-**76**. The spectroscopic data is same with that in the literature [101].

$^1$H NMR δ 7.44 (d, *J* = 7.5Hz, 4H), 7.33 (t, *J* = 7.5Hz, 4H), 7.22 (t, *J* = 7.5Hz), 6.64 (dd, *J* = 6.2Hz, *J* = 1.5Hz, 2H), 4.23 (d, *J* = 6.2Hz, 2H), 1.56 (s, 4H); $^{13}$C NMR δ 147.2, 138.6, 129.6, 128.9, 127.2, 125.2, 40.4, 26.2; HRMS EI: $C_{20}H_{19}$, {$[M+H]^+$}Calc.: 259.1481, Found: 259.1483; $[\alpha]_D^{20}$ = -12.7 (*c* 0.36, $CHCl_3$)

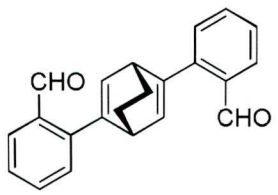
#### (*R*,*R*)-(+)-2,5-di[4'-(methoxycarbonyl)phenyl]bicyclo[2.2.2]octan-2,5-diene (27c)




This compound was prepared according to same procedures from (*R*,*R*)-(-)-**76** described for **(*R*,*R*)-(+)-27a**.

$^1$H NMR δ 8.00(d, *J* = 8.3Hz, 4H), 7.49(d, *J* = 8.3Hz, 4H), 6.79 (dd, *J* = 6.4Hz, *J* = 2.0Hz, 2H), 4.29 (d, *J* = 6.4Hz, 2H), 3.91 (s, 6H), 1.58 (s, 4H); $^{13}$C NMR δ 167.4, 146.4, 142.7, 132.1, 130.3, 128.7, 124.9, 52.5, 40.3, 25.9; HRMS ESI+: $C_{24}H_{22}O_4Na^+$ {$[M+Na]^+$}, Calc.: 397.1416, Found: 397.1418; $[\alpha]_D^{20}$ = +22.5 (*c* 0.28, $CHCl_3$)

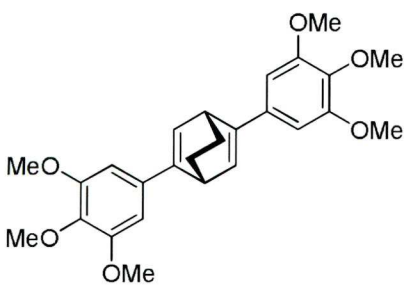
**(*R*,*R*)-(+)-2,5-di[2'-(formyl)phenyl]bicyclo[2.2.2]octan-2,5-diene (27d)**




This compound was prepared according to same procedures from (*R,R*)-(-)-**76** described for **(*R*,*R*)-(+)-27a**.

$^1$H NMR δ 9.98 (s, 2H), 7.86(dd, *J* = 8.4Hz, *J* = 1.4Hz, 2H ), 7.52(dt, *J* = 7.5Hz, *J* = 1.4Hz, 2H ), 7.33 (dt, *J* = 7.5Hz, *J* = 0.6Hz, 2H ), 6.35 (dd, *J* = 6.2Hz, *J* = 2Hz, 2H), 4.01 (dd, *J* = 6.2Hz, *J* = 2Hz, 2H), 1.62 (s, 4H); $^{13}$C NMR δ 192.6, 144.6, 143.8, 136.6, 134.4, 133.9, 128.8, 128.6, 127.8, 44.5, 25.6; HRMS ESI+: $C_{22}H_{18}O_2Na^+$ {[M+Na]$^+$}, Calc.: 337.1204, Found: 337.1204; $[\alpha]_D^{20}$ = +41 (*c* 0.42, $CHCl_3$)

**(*R*,*R*)-(-)-2,5-di{3',4',5'-tri(methoxyl)phenyl}bicyclo[2.2.2]octan-2,5-diene (27e)**

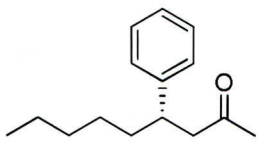



This compound was prepared according to same procedures from (*R,R*)-(-)-**76** described for **(*R*,*R*)-(+)-27a**.

$^1$H NMR δ 6.65(s, 4H), 6.59 (dd, *J* = 6.4Hz, *J* = 2.0Hz, 2H), 4.17 (d, *J* = 6.0Hz, 2H), 3.90 (s, 12H), 3.84 (s, 6H), 1,58(s, 4H); $^{13}$C NMR δ 153.7, 147.4, 137.8, 134.5, 129.2, 102.4, 61.4, 56.6, 40.8, 26.3; HRMS ESI+: $C_{26}H_{30}O_6Na^+$ {[M+Na]$^+$}, Calc.: 461.1940, Found: 461.1944; $[\alpha]_D^{20}$ = -16.5 (*c* 0.35, $CHCl_3$)

### 5.2.4 Chiral products obtained by Rh-diene-catalyzed reactions

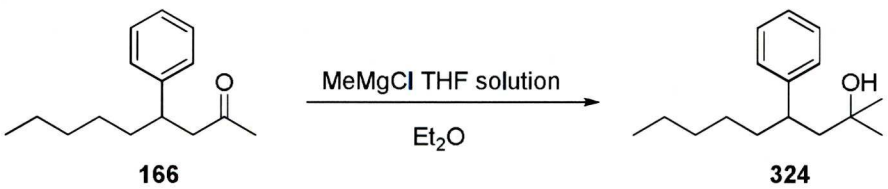
**(*S*)-(+)-3-phenylnonan-2-one ((*S*)-166) (*Table 4.2.2* and entry 4, *Table 4.2.3*)**



The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 99.9 : 0.1, flow = 1.0 mL/min. Retention times: 20.1 min [(*S*)-enantiomer], 21.9 min [(*R*)-enantiomer]. (*R,R*)-**299a** gave 52% e.e., $[\alpha]_D^{20}$ = +9.90 (*c* 0.72, $CHCl_3$); (*R,R*)-**299f** gave 96% e.e., $[\alpha]_D^{20}$ = +17.8 (*c* 0.39, $CHCl_3$), lit [251] ($[\alpha]_D^{20}$ = +17.15° (*c* 1.30, $CHCl_3$) 92% e.e.).

$^1$H NMR δ 7.27-7.29 (m, 2H), 7.15-7.20 (m, 3H), 2.70-3.06 [an ABX system, 3.06-3.14 (m, 1H), 2.71 ( app. d, *J* = 2.0Hz, 1H), 2.70 (app. d, *J* = 1.6Hz, 1H)], 2.00 (s, 3H), 1.53-1.53 (m, 2H), 1.09-1.21 (m, 7H), 0.82 (t, *J* = 7.0Hz, 3H); $^{13}$C NMR: 208.5, 145.0, 128.8, 127.9, 126.7, 51.4, 41.7, 36.8, 32.1, 31.0, 27.4, 22.9, 14.2; HRMS CI: $C_{15}H_{22}O_1{}^+N_1$ {$[M+NH_4]^+$}, Calc.: 236.2009, Found: 236.2012;

Due to the poor reproducibility of the resolution of this compound, the remaining entries were resolved by reacting the compound with methylmagnesiumchloride to give the alcohol derivative (**324**) and subjecting to chiral HPLC with chiralcel OD-H column.




**166** **324**

Protocols for alcohol **324**:

To a 10ml reaction flask, a diethyl ether solution of ketone **166** (2ml, 5mgs / ml, 46μmol) was added and stirred at room temperature. To this solution, methyl magnesium chloride THF solution (22 μL, 68.8 μmol, 3mol / L) was added and stirred

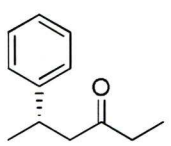
for 5mins. The reaction was quenched by adding 1 ml water to the solution and extracted with diethyl ether (10ml), then dried over anhydrous magnesium sulphate. Filtration followed by evaporation gave the crude product which was purified by preparative TLC (5mgs, 93%).

This compound can be resolved on a chiralcel OD-H column with very good reproducibility. Hexane : IPA = 99.5 : 0.5, 0.5ml / min, Retention times: 41 min [(*R*)-enantiomer], 44 min [(*S*)-enantiomer].

Data for compound **324**

$^1$H NMR δ 7.19-7.24 (m, 3H), 7.09-7.15 (m, 2H), 2.60-2.70 (m, 1H), 1.90 (dd, *J* = 14.2Hz, *J* = 10.0Hz, 1H), 1.75 (dd, *J* = 14.2Hz, *J* = 3.5Hz, 1H ), 1.43-1.56 (m, 4H), 1.09-1.18 (m, 4H), 1.05 (s, 3H), 1.03 (s, 3H), 0.96 (brs, 1H), 0.75 (t, *J* = 6.80Hz, 3H); $^{13}$C NMR: 145.4, 127.5, 126.8, 125.1, 70.5, 49.0, 41.2, 38.1, 30.8, 29.1, 28.7, 26.1, 21.5, 13.0; HRMS CI: $C_{15}H_{22}O_1{}^+N_1$ {$[M+NH_4]^+$}, Calc.: 236.2009, Found: 236.2012;

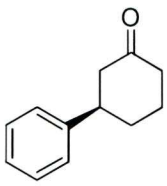
**(*S*)-(+)-5-phenylhexan-3-one ((*S*)-300) (entry 5, *Table 4.2.3*)**



The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 99.5 : 0.5, flow = 0.5 mL/min. Retention times: 19.3 min [(*R*)-enantiomer], 21.5 min [(*S*)-enantiomer]. (*R,R*)-**299a** gave 67% e.e., $[\alpha]_D^{20}$ = +32.4 (*c* 0.68, $CHCl_3$), (*R,R*)-**299f** gave 95%e.e., $[\alpha]_D^{20}$ = +42.7 (*c* 0.48, $CHCl_3$); lit [252] ($[\alpha]_D^{20}$ = -49.58 (*c* = 1.0 in $CHCl_3$) for *R*-enantiomer, 95% e.e.).

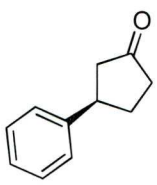
$^1$H NMR δ 7.16-7.31 (m, 5H), 3.29-3.36 (m, 1H), 2.72 (dd, *J* = 16Hz, *J* = 6.5Hz, 1H), 2.62 (dd, *J* = 16Hz, *J* =7.8Hz, 1H), 2.25-2.40 (m, 2H), 1.26 (d, *J* = 7.0Hz, 3H); 0.98 (t, *J* = 7.3Hz, 3H); $^{13}$C NMR δ 210.9, 146.7, 128.9, 127.2, 126.7, 51.2, 37.1, 35.9, 22.4, 8.0; HRMS CI: $C_{12}H_{20}O_1N_1{}^+$ {$[M+NH_4]^+$}, Calc.: 194.1539, Found: 194.1536.

**(*R*)-(+)-3-phenycyclohexanone ((*R*)-147) (entry 1, *Table 4.2.3*)**



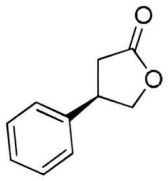
The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 98 : 2, flow = 1.0 mL/min. Retention times: 13.6 min [(*R*)-enantiomer], 14.9 min [(*S*)-enantiomer]. (*R,R*)-**299a** gave 99% e.e., $[\alpha]_D^{20}$ = +20.2 (*c* 0.79, $CHCl_3$), (*R,R*)-**299f** gave 98% e.e., $[\alpha]_D^{20}$ = +20.2 (*c* 0.49, $CHCl_3$); lit [65] $[\alpha]_D^{20}$ =+20.3; $^1H$ NMR δ 7.21-7.36 (m, 5H), 2.97-3.04 (m, 1H), 2.60 (dd, *J* = 14Hz, *J* = 4.5Hz, 1H), 2.54 (d, *J* = 12.5Hz, 1H), 2.34-2.50 (m, 2H), 2.07-2.18 (m, 2H), 1.72-1.91 (m, 2H); $^{13}C$ NMR δ 209.5, 127.2, 125.2, 125.0, 47.4, 43.2, 39.7, 31.2, 24.0; HRMS CI: $C_{12}H_{18}O_1N_1^+$ {$[M+NH_4]^+$}, Calc.: 192.1383, Found: 192.1385.

**(*R*)-(+)-3-phenycyclopentanone ((*R*)-163) (entry 2, *Table 4.2.3*)**



The e.e. was determined on a Daicel Chiralcel OB-H column with hexane: 2-propanol = 99 : 1, flow = 1.0 mL/min. Retention times: 34.3 min [(*S*)-enantiomer], 37.9 min [(*R*)-enantiomer]. (*R,R*)-**299a** gave 99% e.e., $[\alpha]_D^{20}$ = +87.6 (*c* 0.51, $CHCl_3$), (*R,R*)-**299f** gave 96% e.e., $[\alpha]_D^{20}$ = +79.2 (*c* 0.58, $CHCl_3$); lit [65] ( $[\alpha]_D^{25}$=+83.9 (*c* 0.93, $CHCl_3$); $^1H$ NMR δ 7.25-7.37 (m, 5H), 3.42 (m, 1H), 2.67 (dd, *J* = 18Hz, *J* = 8Hz, 1H), 2.26-2.61 (m, 4H), 1.94-2.05 (m, 1H), $^{13}C$ NMR δ 218.8, 143.4, 129.1, 127.1, 46.2, 42.6, 39.3, 31.6; HRMS CI: $C_{11}H_{16}O_1N_1^+$ {$[M+NH_4]^+$}, Calc.: 178.1226, Found: 178.1227;

**(*R*)-(-)-3-phenylbutyrolactone ((*R*)-164) (entry 3, *Table 4.2.3*)**



The e.e. was determined on a Daicel Chiralcel AD-H column with hexane: 2-propanol = 98 : 2, flow = 1.0 mL/min. Retention times: 25.6 min [(*S*)-enantiomer], 28 min [(*R*)-enantiomer]; $[\alpha]_D^{20}$ = -45.4 (*c* 0.39, $CHCl_3$) for (*R,R*)-**299a**, $[\alpha]_D^{20}$ = -43.5 (*c* 0.44, $CHCl_3$) for (*R,R*)-**299f**; lit [250] ($[\alpha]_D^{20}$ =+38.4 (*c* 1.0, $CHCl_3$) for (*S*)-enantiomer with 81%e.e.).

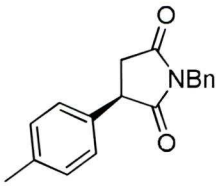
$^1$H NMR δ 7.23-7.39 (m, 5H), 4.67 (t, *J* = 8Hz, 1H), 4.27 (t, *J* = 8Hz, 1H), 3.80 (m, 1H), 2.93 (dd, *J* = 18Hz, *J* = 9.0, 1H), 2.68 (dd, *J* = 18Hz, *J* = 9.0Hz, 1H); $^{13}$C NMR δ 139.8, 129.6, 128.1, 127.1, 74.4, 41.5, 36.1; HRMS CI: $C_{10}H_{14}O_2N_1^+$ {$[M+NH_4]^+$}, Calc.: 180.1019, Found: 180.1018.

**(*R*)-(-)-3-phenyl-*N*-benylmaleimide ((*R*)-174a) (entry 1, *Table 4.2.4*)**


The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 23.0 min [(*S*)-enantiomer], 29.3 min [(*R*)-enantiomer], 95% e.e., $[\alpha]_D^{20}$ = -37.6 (*c* 0.31, $CHCl_3$); Lit [107] ($[\alpha]_D^{20}$ = -33.7 (*c* 1.20, $CHCl_3$), 69% e.e.).

$^1$H NMR δ 7.27-7.41 (m, 7H), 7.15 (d, *J* = 7.0Hz, 2H), 4.75 (d, *J* = 14Hz, 1H), 4.69 (d, *J* = 14Hz, 1H), 4.01 (dd, *J* = 9.5Hz, *J* = 5.0Hz, 1H), 3.20 (dd, *J* = 18.5Hz, *J* = 9.5Hz, 1H), 2.82 (dd, *J* = 18.5, *J* = 5.0Hz, 1H); $^{13}$C NMR δ 177.8, 176.2, 137.6, 136.2, 129.6, 129.2, 129.1, 128.4, 128.4, 127.8, 46.3, 43.1, 37.6; HRMS: $C_{17}H_{15}N_1O_2Na^+$ {$[M+Na]^+$}, Calc.: 288.1000, Found: 288.1002.

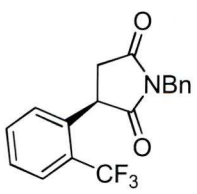
**(*R*)-(-)-3-(4-methylphenyl)-*N*-benylmaleimide ((*R*)-174b) (entry 2, *Table 4.2.4*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 22.3 min [(*S*)-enantiomer], 25.3 min [(*R*)-enantiomer],96% e.e. Absolute configuration was assigned by analogy with (*R*)-**174a**. $[\alpha]_D^{20}$ = -53.6 (*c* 0.38, $CHCl_3$).

$^1$H NMR δ 7.25-7.41 (m, 5H), 7.14 (d, *J* = 8Hz, 2H), 7.03 (d, *J* = 8Hz, 2H), 4.73 (d, *J* = 14Hz, 1H), 4.68 (d, *J* = 14Hz, 1H), 3.96 (m, 1H), 3.17 (dd, *J* = 18.5Hz, *J* = 9.5Hz, 1H), 2.79 (dd, *J* = 18.5Hz, *J* = 5.0Hz, 1H); $^{13}$C NMR δ 178.0, 176.3, 138.1, 136.2, 134.5, 130.2, 129.2, 129.1, 128.4, 127.6, 45.9, 43.1, 37.6, 21.5; HRMS: $C_{18}H_{17}N_1O_2Na^+$ {$[M+Na]^+$}, Calc.: 302.1157, Found: 302.1150.

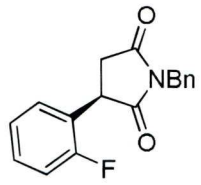
**(*R*)-(+)-3-(2-trifluoromethylphenyl)-*N*-benylmaleimide ((*R*)-174c) (entry 3, *Table 4.2.4*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 13.6 min [(*S*)-enantiomer], 15.4 min [(*R*)-enantiomer], 99% e.e. Absolute configuration was assigned by analogy with (*R*)-**174a**. $[\alpha]_D^{20}$ = +59.2 (*c* 0.41, $CHCl_3$).

$^1$H NMR δ 7.69 (d, *J* = 7.8Hz, 1H), 7.28-7.51 (m, 7H), 7.00 (d, *J* = 7.7Hz), 4.79 (d, *J* = 14Hz, 1H), 4.75 (d, *J* = 14Hz, 1H), 4.44 (dd, *J* = 10Hz, *J* = 5Hz, 1H), 3.26 (dd, *J* = 18Hz, *J* = 10Hz, 1H), 2.62 (dd, *J* = 18Hz, *J* = 5Hz, 1H); $^{13}$C NMR: δ: 177.4, 175.6, 136.1, 133.4, 129.4, 129.2, 128.6, 128.4, 128.3, 126.8, 43.3, 42.9, 39.2; HRMS: $C_{18}H_{14}N_2O_3F_3Na^+$ {$[M+Na]^+$}, Calc.: 358.0874, Found: 358.0877;

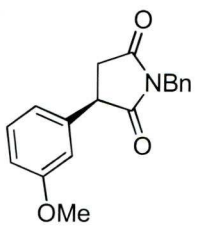
**(*R*)-(-)-3-(2-fluorophenyl)-*N*-benylmaleimide ((*R*)-174d) (entry 4, *Table 4.2.4*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 21.1 min [(*S*)-enantiomer], 33.5 min [(*R*)-enantiomer], 96% e.e. Absolute configuration was assigned by analogy with (*R*)-**174a**. $[\alpha]_D^{20}$ = -6.64 (*c* 0.76, $CHCl_3$).

$^1H$ NMR δ 7.27-7.43(m, 6H), 7.04-7.17(m, 3H), 4.78(d, *J* = 14Hz, 1H), 4.72(d, *J* = 14Hz, 1H), 4.10 (dd, *J* = 10Hz, *J* = 5.5Hz, 1H), 3.19 (dd, *J* = 18Hz, *J* = 10Hz, 1H), 2.76 (dd, *J* = 8Hz, *J* = 5.5Hz, 1H); $^{13}C$ NMR δ 177.2, 175.8, 161.1 (d, *J* = 580Hz), 136.0, 130.5 (d, *J* = 15.6Hz), 130.3 (d, *J* = 33Hz), 129.1 (d, *J* = 42Hz), 128.4, 125.1, 125.1, 125.0 (d, *J* = 54Hz); (HRMS: $C_{17}H_{14}N_1O_2F_1Na^+$ {$[M+Na]^+$}, Calc.: 306.0906, Found: 306.0907;

**(*R*)-(-)-3-(3-methoxyphenyl)-*N*-benylmaleimide ((*R*)-174e) (entry 5, *Table 4.2.4*)**

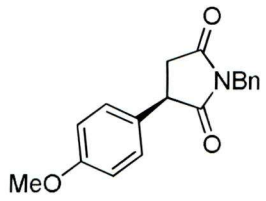



The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 36.0 min [(*S*)-enantiomer], 48.1 min [(*R*)-enantiomer], 96% e.e. Absolute configuration was assigned by analogy with (*R*)-**174a**. $[\alpha]_D^{20}$ = -44.1 (*c* 0.55, $CHCl_3$).

1H NMR δ 7.22-7.40 (m, 6H), 6.81 (dd, *J* = 8Hz, *J* = 2.5Hz, 1H), 6.72 (d, *J* = 8.0Hz, 1H), 6.66 (d, *J* = 1.8Hz, 1H), 4.74 (d, *J* = 14Hz, 1H), 4.68 (d, *J* = 14Hz, 1H), 3.73 (s, 3H), 3.18 (dd, *J* = 18.5Hz, *J* = 9.5Hz, 1H), 2.79 (dd, *J* = 18.5Hz, *J* = 9.5Hz, 1H); $^{13}C$

NMR 177.7, 176.2, 160.5, 139.1, 136.2, 130.6, 129.2, 129.1, 128.4, 119.9, 113.8, 113.5, 55.6, 46.3, 43.1, 37.6; HRMS: $C_{18}H_{17}N_1O_3Na^+$ {[M+Na]$^+$}, Calc.: 318.1106, Found: 318.1098.

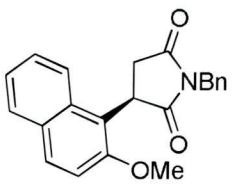
**(*R*)-(+)-3-(4-methoxyphenyl)-*N*-benylmaleimide ((*R*)-174f) (entry 6, *Table 4.2.4*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane : 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 36.6 min [(*R*)-enantiomer], 43.5 min [(*S*)-enantiomer], 99% e.e., $[\alpha]_D^{20}$ = -59.8 (*c* 0.42, $CHCl_3$), lit [79] $[\alpha]_D^{20}$ = +57.6 (*c* 0.77, $CHCl_3$) for *S*-enantiomer;

$^1$H NMR δ 7.37 (d, *J* = 6Hz, 2H), 7.29-7.34 (m, 3H), 7.07 (d, *J* = 8.6Hz, 2H), 6.86 (d, *J* = 8.6Hz, 2H), 4.74 (d, *J* = 14Hz, 1H), 4.75 (d, *J* = 14Hz, 1H), 3.96 (dd, *J* = 9.5Hz, *J* = 5.0Hz, 1H), 3.78 (s, 3H), 3.17 (dd, *J* = 18.5Hz, *J* = 9.5Hz, 1H), 2.78 (dd, *J* = 18.5Hz, *J* = 5.0Hz, 1H); $^{13}$C NMR δ 178.1, 176.3, 159.6, 136.2, 129.5, 129.2, 129.1, 128.8, 128.4, 115.0, 55.7, 45.5, 43.1, 37.6; HRMS: $C_{18}H_{17}N_1O_3Na^+$ {[M+Na]$^+$}, Calc.: 318.1106, Found: 318.1095;

**(*R*)-(-)-3-(2-methoxynaphthy-1-l)-*N*-benylmaleimide ((*R*)-174g) (entry 7, *Table 4.2.4*)**

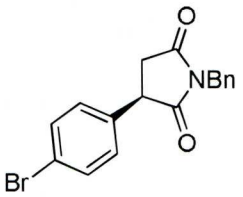



The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 70 : 30, flow = 1.0 mL/min. Retention times: 25.5 min [(*R*)-enantiomer], 51.5 min [(*S*)-enantiomer], 100% e.e. Absolute configuration was assigned by analogy with

(*R*)-**174a**. $[\alpha]_D^{20}$ = -10.0 (*c* 0.39, $CHCl_3$).

$^1$H NMR δ 7.88 (d, *J* = 4.6Hz, 1H), 7.80 (d, *J* = 9Hz, 2H), 7.49-7.77 (m, 3H), 7.24-7.38 (m, 4H), 7.16 (d, *J* = 9Hz, 1H), 4.81 (d, *J* = 13.5Hz, 1H), 4.75 (d, *J* = 13.5Hz, 1H), 4.65 (dd, *J* = 9.5Hz, *J* = 5.6Hz, 1H), 3.31 (s, 3H), 3.16 (dd, *J* = 18Hz, *J* = 9.5Hz, 1H), 2.72 (dd, *J* = 18Hz, *J* = 5.6Hz, 1H); $^{13}$NMR δ 179.3, 176.9, 154.8, 136.8, 133.4, 130.3, 130.0, 129.6, 129.3, 129.0, 128.3, 127.7, 124.1, 122.0, 119.2, 113.4, 55.9, 43.1, 38.7, 36.9; HRMS: $C_{22}H_{19}N_1O_3Na$ {$[M+Na]^+$}, Calc.: 368.1263, Found: 368.1260.

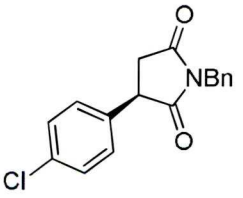
**(*R*)-(-)-3-(4-bromophenyl)-*N*-benylmaleimide ((*R*)-174h) (entry 8, *Table 4.2.4*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 90 : 10, flow = 1.0 mL/min. Retention times: 39.2 min [(*S*)-enantiomer], 42.7 min [(*R*)-enantiomer], 91% e.e. Absolute configuration was assigned by analogy with (*R*)-**174a**. $[\alpha]_D^{20}$ = -38.4 (*c* 0.41, $CHCl_3$).

$^1$H NMR δ 7.46 (d, *J* = 8Hz, 2H), 7.28-7.40 (m, 5H), 7.03 (d, *J* = 8Hz, 2H), 4.73 (d, *J* = 14Hz, 1H), 4.68 (d, *J* = 14Hz, 1H), 3.97 (dd, *J* = 9.5Hz, *J* = 5.0Hz, 1H), 3.19 (dd, *J* = 18.5, *J* = 9.5, 1H), 2.76 (dd, *J* = 18.5, 5.0Hz, 1H); $^{13}$C NMR: 177.3, 175.8, 136.4, 136.0, 132.7, 129.5, 129.3, 129.2, 128.5, 122.4, 45.7, 43.2, 37.3; HRMS ESI+: $C_{17}H_{14}N_1O_2Br_1Na^+$ {$[M+Na]^+$}, Calc.: 366.0106, Found: 366.0089.

**(*R*)-(-)-3-(4-chlorophenyl)-*N*-benylmaleimide ((*R*)-174i) (entry 9, *Table 4.2.4*)**

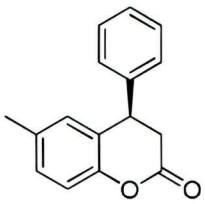



The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol

= 90 : 10, flow = 1.0 mL/min. Retention times: 34.7 min [(*S*)-enantiomer], 37.7 min [(*R*)-enantiomer], 92% e.e. Absolute configuration was assigned by analogy with (*R*)-**174a**. $[\alpha]_D^{20}$ = -42.8 (*c* 0.31, $CHCl_3$).

1H NMR δ 7.30-7.40 (m, 7H), 7.09 (d, *J* = 8Hz, 2H), 4.74 (d, *J* = 14, 1H), 4.68 (d, *J* = 14, 1H), 3.99 (dd, *J* = 9.5, *J* = 5.0, 1H), 3.20 (dd, *J* = 18.5, *J* = 9.5, 1H), 2.77 (dd, *J* = 18.5, *J* = 5.0); $^{13}C$ NMR δ 177.4, 175.8, 136.0, 135.9, 134.4, 129.8, 129.3, 129.2, 128.6, 45.6, 43.2, 37.3; HRMS ESI+: $C_{17}H_{14}N_1O_2Cl_1Na^+$ {$[M+Na]^+$}, Calc.: 322.0611, Found: 322.0601.

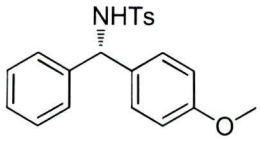
**(*R*)-(-)-3-phenyl-6-methyl-dihydrocoumarin ((*R*)-303) (*Table 4.2.4*)**



The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 98 : 2, flow = 1.0 mL/min. Retention times: 15.5 min [(*S*)-enantiomer], 18.6 min [(R)-enantiomer], (*R,R*)-**299g** (table 4.2.5, entry 2): 98% e.e. $[\alpha]_D^{20}$ = -2.24 (*c* 0.35, $CHCl_3$), (*R,R*)-**29** (table 4.2.5, entry 4): 98% e.e. $[\alpha]_D^{20}$ = -2.20 (*c* 0.33, $CHCl_3$), (*R,R*)-**299a** (table 4.2.5, entry 6): $[\alpha]_D^{20}$ = -2.25 (*c* 0.32, $CHCl_3$), (*R,R*)-**299e** (table 4.2.5, entry 8): 98% e.e. $[\alpha]_D^{20}$ = -2.33 (*c* 0.68, $CHCl_3$).The absolute configuration was compared with lit [199] ($[\alpha]_D^{20}$ = - 6.0 (*c* 1.0, $CHCl_3$), 99% e.e.).

1H NMR δ 7.35 (t, *J* =7.0Hz, 2H), 7.30 (d, *J* = 7.0Hz, 1H), 7.15 (d, *J* = 7.0Hz, 2H), 7.09 (d, *J* = 8.0Hz, 1H), 7.02 (d, *J* = 8.0Hz, 1H), 6.78 (s, 1H), 4.30 (t, *J* = 6.8Hz, 1H), 3.06 (d of AB system, *J* = 15.8Hz, *J* =6.1Hz, 1H), 3.00 (d of AB system, *J* = 15.8Hz, *J* = 7.4Hz, 1H), 2.26 (s, 3H); $^{13}C$ NMR δ 168.3, 150.1, 140.9, 134.8, 129.7, 129.5, 129.1, 128.0, 127.9, 125.7, 117.3, 41.2, 37.6, 21.2; HRMS ESI+: $C_{16}H_{14}O_2Na^+$ {$[M+Na]^+$}, Calc.: 261.0891, Found: 261.0895;

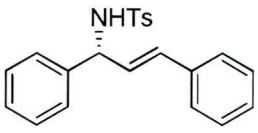
**(*S*)-(+)-1-phenyl-1-(4-methoxyphenyl)-N-tosyl-methylamine ((*S*)-179ag, *Scheme 4.2.3*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 70 : 30, flow = 0.7 mL/min. Retention times: 11.1 min [(*R*)-enantiomer], 17.5 min [(*S*)-enantiomer]. (*R,R*)-**299a**: 35% e.e. $[\alpha]_D^{20}$ = +6.62 (*c* 0.31, $CHCl_3$), (*R,R*)-**299f**: 94% e.e. $[\alpha]_D^{20}$ = +17.80 (*c* 0.54, $CHCl_3$),

$^1H$ NMR δ 7.48 (d, *J* = 8.2Hz, 2H), 7.10-7.14 (m, 3H), 7.06 (d, *J* = 8.2Hz, 2H), 7.02-7.05 (m, 2H), 6.92 (d, *J* = 8.7Hz, 2H), 6.65 (d, *J* = 8.7Hz, 2H), 5.44 (d, *J* = 6.9Hz, 1H), 5.03 (d, *J* = 6.9Hz, 1H); 3.68 (s, 3H), 2.30 (s, 3H); $^{13}C$ NMR δ 159.9, 142.1, 139.7, 136.4, 131.7, 128.3, 127.58, 127.47, 127.45, 126.24, 126.19, 112.9, 59.8, 54.2, 20.5; HRMS: $C_{21}H_{21}N_1O_3S_1Na^+$ {$[M+Na]^+$}, Calc.: 390.1140, Found: 390.1144

**(*R*)-(*E*)-(+)-*N*-(1,3-diphenylpropen-2-yl)-4-methylbenzenesulfonamide ((*S*)-316aa, entry 12, *Table 4.2.6*)**




Reaction procedure for **(*S*)-316aa**:

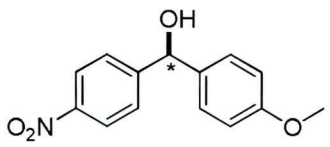
To a Sclenck reaction tube, $[Rh(C_2H_4)Cl]_2$ (1.8mg, 9.0 mol), chiral diene ligand (3.74 mg, 10.0 mol) and 0.2ml anhydrous toluene were added and stirred at 50°C for 10mins. The resulting solution was diluted with toluene (0.8ml) followed addition of *N*-toslyimine (75mg, 0.3mmol), potassium stryenyl trifluoroborate (120mg, 0.6mmol) and then triethylborane hexane solution (0.3ml, 0.3mmol, 1.0 M). The reaction mixture was stirred at 50°C for 6hrs. 10% HCl aqueous solution (1ml) was added to the reaction mixture and stirred for 20min. The mixure was diluted by diethyl ether (10ml) and water (10ml) and then subjected to a separating funnel to extract. The mixture was extracted with EtOAc (3 × 10 mL), extracts were combined and washed with water, 1N NaOH, water and brine in turn then dried over $Na_2SO_4$. After filtration and evaporation the crude product was purified by silica column

chromatography (Hexane:EtOAc; 5:1) to give pure product **(*S*)-316aa** (81% yield, 99% e.e.)

The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 80 : 20, flow = 0.5 mL/min. Retention times: 22 min [(*S*)-enantiomer], 27 min [(*R*)-enantiomer]. (*R,R*)-**27d**: 81% yield, 99% e.e., $[\alpha]_D^{20}$ = +34.0, (*c* 1.0, $CHCl_3$), The absolute configuration was consistent with lit [253] ($[\alpha]_D^{20}$ = + 25.6 (*c* 0.8, $CHCl_3$), 75.6% e.e.).;

$^1$H NMR δ 7.65–7.67 (m, 2H), 7.13–7.28 (m, 12H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.07 (dd, *J* = 6.8, *J* = 15.6 Hz, 1H), 5.11 (t, *J* = 7.2 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 2.32 (s, 3H), $^{13}$C NMR δ 143.5, 139.8, 137.8, 136.2, 132.4, 129.6, 128.9, 128.6, 128.3, 128.1, 127.5, 127.2, 126.7, 59.9, 21.6.

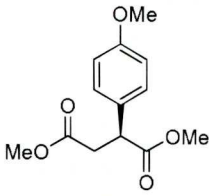
**(4-methoxyphenyl)(4-nitrophenyl)methanol (184ag, entry 1, *Table 4.2.7*)**




The e.e. was determined on a Daicel Chiralcel OD-H column with hexane: 2-propanol = 70 : 30, flow = 0.7mL/min. Retention times, 26.0 min, 39 min (absolute configuration was not assigned).

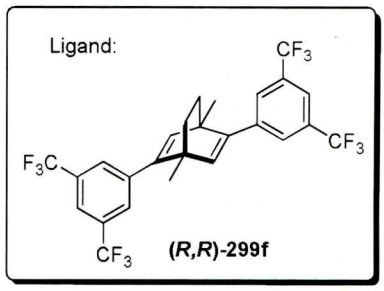
$^1$H NMR δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.55 (d,*J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.86 (s, 1H), 3.78 (s, 3H), 2.48 (brs, 1H); $^{13}$C NMR δ 2159.6, 151.1, 147.1, 135.0, 128.1, 127.0, 123.6, 114.3, 75.1, 55.3; HRMS ESI+: $C_{14}H_{13}NO_4Na^+$ {$[M+Na]^+$}, Calc.: 282.0742, Found: 282.0738.

**(*S*)-(-)-dimethyl(4-methoxyphenyl)succinate and (*R*)-(+)-dimethyl(4-methoxyphenyl)succinate (322)**



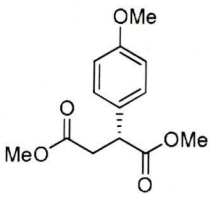

(*S*)-**323**

From dimethyl fumarate and catalyzed by (*R,R*)-**299f**




Gave opposite configurations

$[\alpha]_d^{20}$ = -97° (*c* 1.15, $CHCl_3$), 80% ee

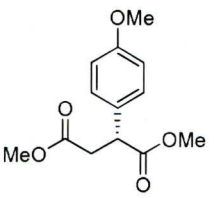



(*R*)-**323**

From dimethyl maleate and catalyzed by (*R,R*)-**299f**

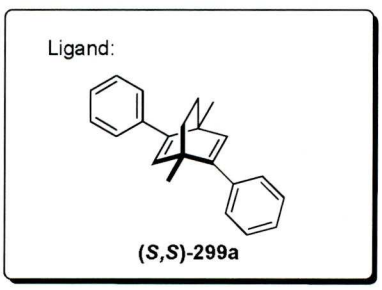
$[\alpha]_d^{20}$ = +88.6° (*c* 1.10, $CHCl_3$), 70% ee

( Products in ***Scheme 4.2.4***, Chapter 4)



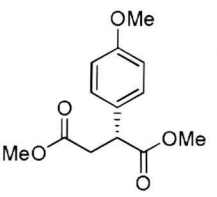

(*R*)-**323**

From dimethyl fumarate and catalyzed by (*S,S*)-**299a**




Gave same configurations

$[\alpha]_d^{20}$ = +102° (*c* 0.84, $CHCl_3$), 88% ee




(*R*)-**323**

From dimethyl maleate and catalyzed by (*S,S*)-**299a**

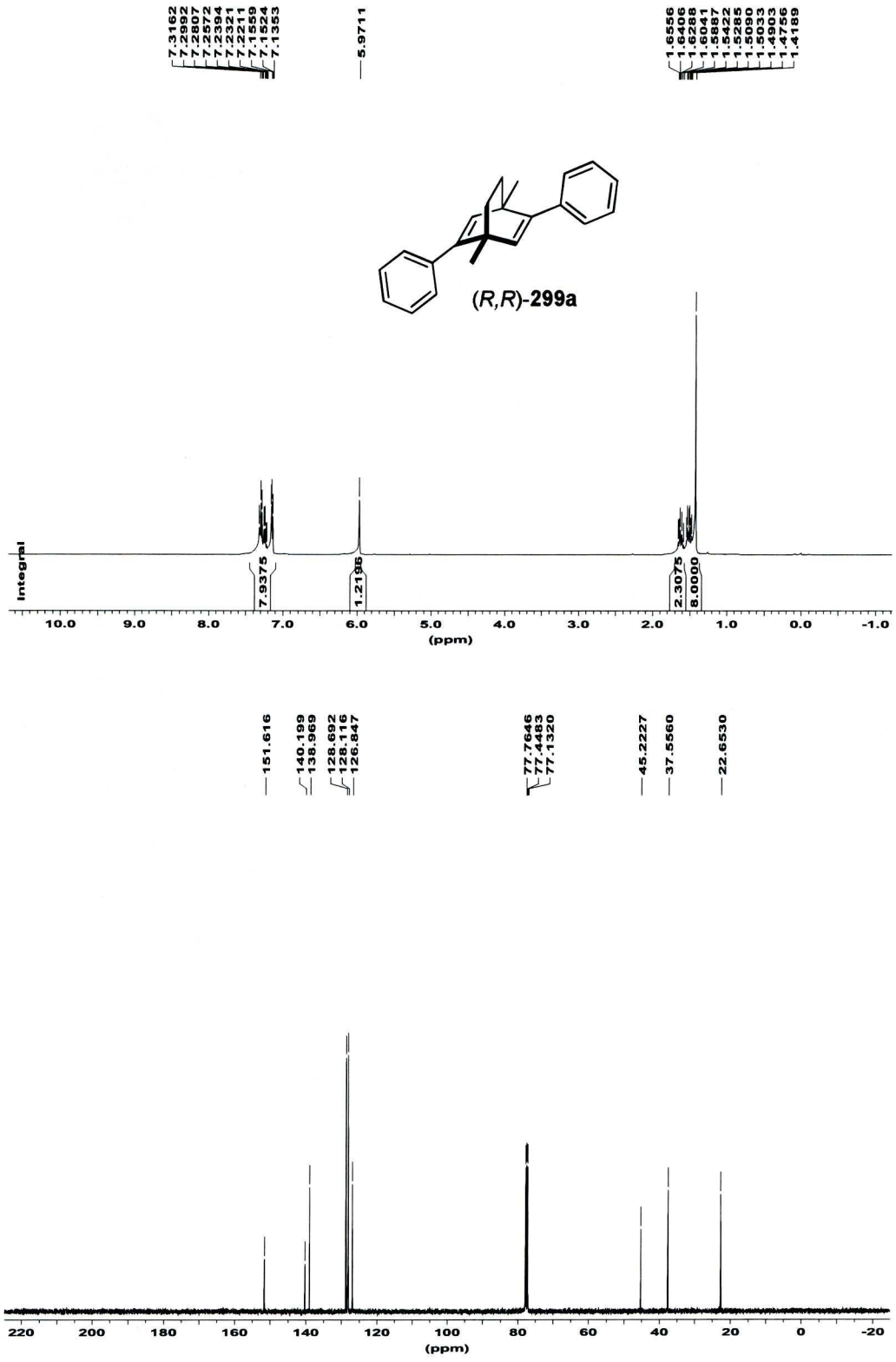
$[\alpha]_d^{20}$ = +29° (*c* 1.10, $CHCl_3$), 27% ee

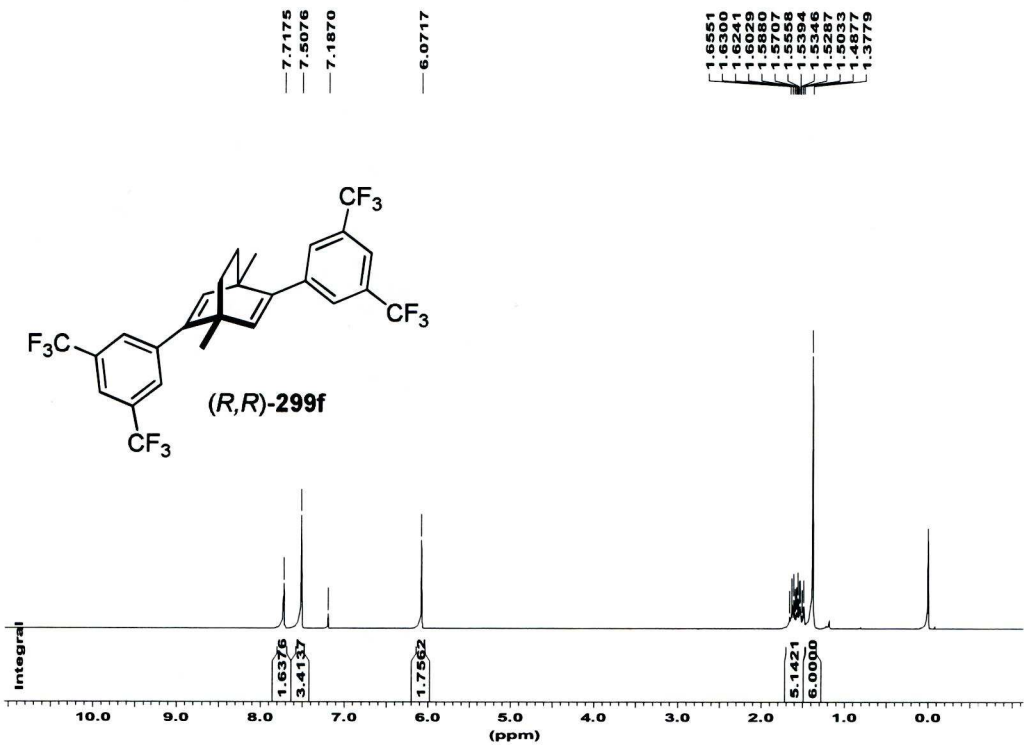
( Products in ***Scheme 4.2.5***, Chapter 4)

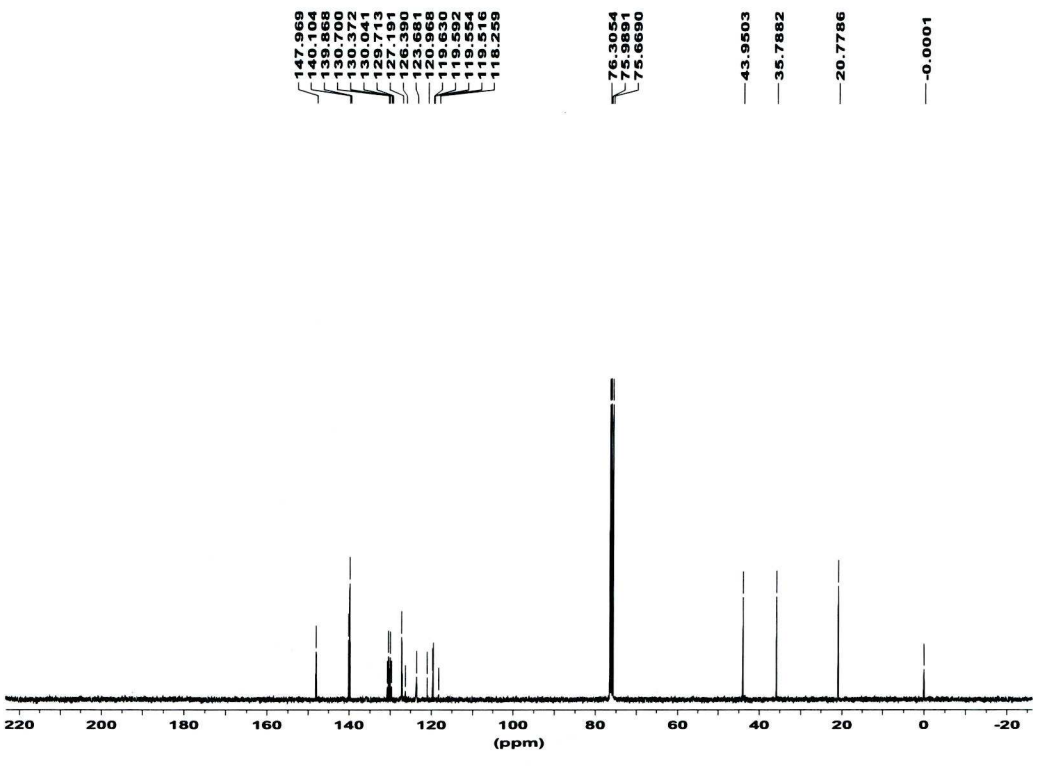
The e.e. was determined on a Daicel Chiralcel OJ-H column with hexane: 2-propanol = 98 : 2, flow = 1.0 mL/min. Retention times: 29.6 min [(*S*)-enantiomer], 33.7 min [(*R*)-enantiomer].

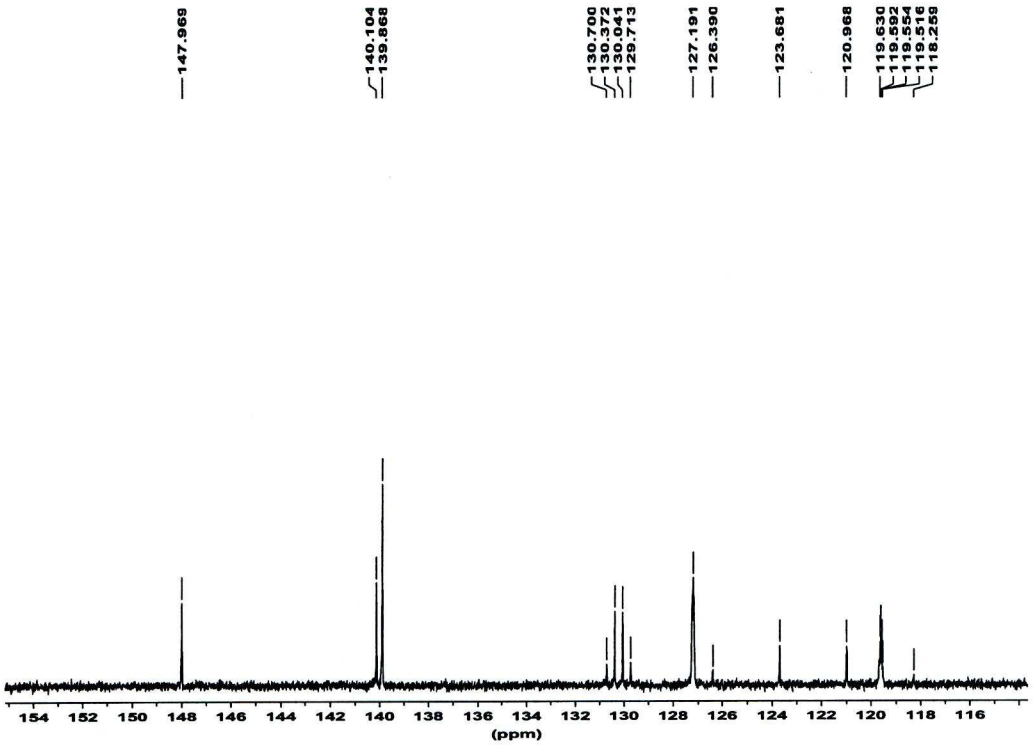
$^{1}$H NMR : 7.12 (d, $J$ = 9 Hz, 2H), 6.78 (d, $J$ = 9 Hz, 2H), 3.97 (dd, $J$ = 10 Hz, $J$ = 5.6 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.59 (s, 3H), 3.10 (dd, $J$ = 17 Hz, $J$ = 10 Hz, 1H), 2.58 (dd, $J$ = 17 Hz, $J$ = 5.6 Hz, 1H); $^{13}$C NMR : 172.6, 171.0, 158.0, 128.6, 127.7, 113.2, 54.2, 51.3, 50.8, 45.2, 36.7; HRMS ESI+: $C_{13}H_{16}O_5Cl_1Na^+$ {$[M+Na]^+$}, Calc.: 275.0895, Found: 275.0889.

## 5.3 NMR spectrum (sample)




7.7175
7.5076
7.1870
6.0717
1.6551
1.6300
1.6241
1.6029
1.5880
1.5707
1.5558
1.5394
1.5346
1.5287
1.5033
1.4877
1.3779
CF3
CF3
F3C
CF3
(R,R)-299f
Integral
1.6376
3.4137
1.7562
5.1421
6.0000
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


147.969
140.104
139.868
130.700
130.372
130.041
129.713
127.191
126.390
123.681
120.968
119.630
119.592
119.554
119.516
118.259
76.3054
75.9891
75.6690
43.9503
35.7882
20.7786
-0.0001
220
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)




Expanded $^{13}C$ NMR spectrum of (*S,S*)-7 from 115 to164 ppm

# Chapter 6 References

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# A Practical Chemo-enzymatic Synthesis of Homochiral Bicyclo[2.2.2]octane-2,5-dione

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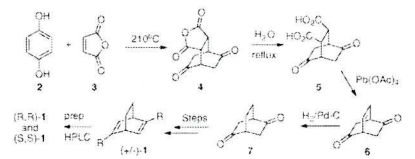
A practical synthetic route for the preparation of chiral bicyclo[2.2.2]octane-2,5-dione, the precursor of useful chiral diene ligands, was realized via Diels−Alder reaction and resolution of an enol acetate derivative by immobilized lipases.

Chiral diene ligand complexes[1] of rhodium are highly effective catalysts for the asymmetric addition of arylboronic acids to α,β-unsaturated ketones,[2] asymmetric arylation of *N*-tosylarylamines,[3] arylative cyclization of alkynals,[4] and intramolecular asymmetric [4 + 2] cycloaddition of alkyne-1,3,-dienes.[5] Complexes with iridium are used for resolution of allyl carbonates.[6] The $C_2$-symmetric 2,5-disubstituted bicyclo[2.2.2]octane-2,5-dienes **1** developed by Hayashi (Scheme 1) have shown particular versatility. The bicyclic 2,5-diene is also a starting material for synthesis of CNS-modulators.[7] The chiral diketones **7**, synthetic precursors to

SCHEME 1. Existing Synthetic Route to Chiral Diene Ligands 1




the diene compounds, are difficult to access both in terms of synthesis and resolution and this may have limited widespread application of chiral diene ligands in asymmetric catalysis. For the synthesis of racemic **7**, the most frequently used route (Scheme 1) is low yielding (overall 4%): Diels−Alder reaction of hydroquinone **2** with maleic anhydride **3** gives compound **4**, which upon hydrolysis gives the diacid **5**. The decarboxylation step affords compound **6** in low yield (14%) which is then hydrogenated to give compound **7**.

A number of approaches have been taken for resolution of the diketone or its synthetic prescursors. The unsaturated dione **6** has been resolved as diastereomeric diethyl (*R,R*)-(+)-tartrate acetals[8] and as an inclusion complex with (*S*)-(−)-(10,10′)-dihydroxy-9,9-biphenanthryl,[9] and the diacid **5** was resolved as its brucine salt, followed by electrolysis to give (−)-**6**.[8,10] Furthermore a chiral dihydrazone of compound **7** was resolved by fractional recrystallization.[2a] However, all these methods were inefficient for multigram preparation.

Naemura investigated resolution of bicyclo[2.2.1]heptane-, bicyclo[2.2.2]octane-, and bicyclo[3.2.1]octanediols by lipase-catalyzed transesterification or hydrolysis reactions. The best result for the hydrolysis of the diacetate of *endo,endo*-2,5-dihydroxybicyclo[2.2.2]heptane was 29% yield and 84% ee.[11a] The lipase YS catalyzed transesterification on the diols was only successful for the [3.3.1] system and gave no improvement for the [2.2.2] system.[11b] Racemic diketone **6** was resolved by baker's yeast reduction to give hydroxyketone and unreacted (+)-ketone **6** with varying ee's depending on the incubation time.[10] Frejd et al. developed a route to chiral diketone **7** using a 1,2-carbonyl transposition starting from (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one in nine steps.[12a] One notable result has been reported by the same group recently: compound **7** was reduced to a diastereomeric

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mixture of hydroxy ketones in 98% conversion and 99% ee for each diasteroisomer by using genetically engineered *Saccharomyces cerevisiae*.[12b] However, this approach suffered from low substrate concentrations and separation problems. In practice, the homochiral diene ligands are prepared by preparative chiral HPLC resolution (Chiralcel OJ) of the diketone, the diene, or a bis enol triflate intermediate.[2a]

We have been exploring alternative synthetic routes and resolution methods for accessing diketone **7** in order to make the diene ligands and thus the asymmetric transformations more accessible to the synthetic community. Herein, we provide a practical chemoenzymatic route to homochiral diketone **7**. The key step is a lipase-catalyzed resolution of the (±)-enol acetate **13**, derived from the diketone **7** (Scheme 2). Solvent screening, choice of immobilization material, and optimization of reaction conditions has resulted in the indentification of enantiocomplementary biotransformations to access either enantiomer of diketone **7** in homochiral form.

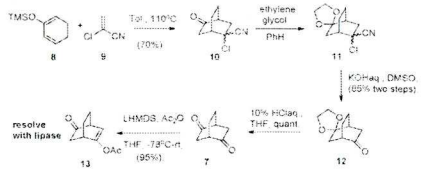
The bicyclic [2.2.2] system was constructed by [4 + 2] cycloaddition of 2-(trimethylsiloxy)-1,3-cylcohexadiene **8** and 2-chloroacrylonitrile **9**.[12c] The major product was the desired 2,5-adduct **10**, after cleavage of the intermediate enol silyl ether which apparently occurs in situ. The ketone group in compound **10** was protected with ethylene glycol to give **11** prior to hydrolysis to afford the monoacetal **12**[13] (two steps 85% yield). Hydrolysis of the ketal group with 10% HCl/THF at room temperature afforded racemic diketone **7** in quantitative yield. This route thus provides the diketone **7** in an overall 60% yield for four steps.

We have previously developed lipase-catalyzed resolutions of enol acetates as an effective alternative to asymmetric enolate formation for the desymmetrisation of prochiral ketones (Scheme 3).[14] The enol acetate **14** was resolved with *Pseudomonas fluorescens* lipase (PFL) to provide a key building block for the synthesis of NK-2 antagonists.[15] Similarly oxabicyclic enol ester **15** was resolved with high selectivity using silica-absorbed *Humicola* sp. lipase.[16]

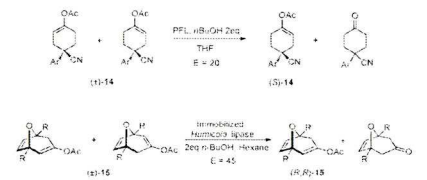
Thus, we envisioned a resolution of enol acetate **13** as a way of obtaining optically pure diketone **7**. Our previously employed PFL in THF gave no reaction, while silica-absorbed *Humicola* sp. lipase in hexane gave low selectivity. An initial screen of lipases was carried with various solvents. Only *Candida antarctica* lipase (Cal-B) showed moderate enantioselectivity in toluene ($E$ = 15), albeit with a very low reaction rate.

Given our earlier success with immobilized *Humicola* sp. lipase for the bicyclic compound **15**, investigation was focused on this enzyme (Table 1). Solvent screening showed that the silica-absorbed *Humicola* sp. lipase[16] works best in hydrophobic solvents, with pentane giving the highest initial $E$ value of 15 (entry 5). The lyophilized enzyme gave lower selectivity although this could be improved by the presence of a small amount of water (5 equiv) (entry 6 vs 7). The commercially supplied enzyme in phosphate buffer gave very

SCHEME 2. Preparation of Bicyclo[2.2.2]octane-2,5-dione 7 and Corresponding Enol Acetate 13




SCHEME 3. Lipase-Catalyzed Resolution of Cyclic Enol Acetates




low selectivity (entry 8). Use of the protein-coated microcrystal prepared according to Kreiner[17] led to an increased rate of conversion but lower selectivity (entry 9).

Exciting results were obtained with the enzyme immobilized on the hydrophobic supports Accurel[18] or PhosES-03 (PhosphonicS) in pentane (entries 13 and 14), where the $E$ values were as high as 68 and 116, respectively. This high selectivity depended on the presence of residual water in the immobilized enzyme from the immobilization process. Accurel is polypropylene powder with ca. 250 μm particle size, with a large hydrophobic surface to which the enzyme adsorbs; PhosES-03 is functionalized silica with a high degree of hydrophobic surface modification and covalent linkage to the enzyme.

Silica, sol−gel,[19] and PhosES-01 (entries 5, 10, and 11) all contain no surface modification and gave lower $E$ values than entries 13 and 14. The supporting silica PhosES-02 (entry 12) is partially modified (less than PhosES-03) with surface hydrophobic groups, and in this case, the $E$ value of 40 was intermediate between entries 5, 10, 11 and entries 13 and 14. Interestingly, the widely used Eupergit[19] support gave disappointing selectivity (entries 16 and 17), which may be explained by the relatively polar amino alcohol residues generated at the point of enzyme attachment to the resin. These results indicate that the more hydrophobic the support surface, the better the enantioselectivity of the enzyme for this biotransformation. This could be attributed to a conformational change within the active site. Biophysical studies using solid-state IR spectroscopy indicate that the hydrophobic lid that covers the active site of *Humicola* sp. lipase is

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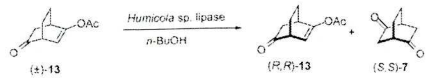
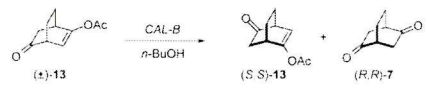
**TABLE 1. Screening *Humicola* sp. Lipase**




| entry[a] | solvents | immobilization | conversion[c] (%) | (R,R)-enol ester 13 ee[d] (%) | reaction time | *E* value |
|---|---|---|---|---|---|---|
| 1 | hexane | silica[e] | 60 | 73 | 2 d | 6 |
| 2 | cyclohexane | silica[e] | 31 | 28 | 1 d | 5 |
| 3 | heptane | silica[e] | 29 | 27 | 1 d | 6 |
| 4 | petroether | silica[e] | 27 | 26 | 1 d | 5 |
| 5 | pentane | silica[e] | 31 | 37 | 1 d | 15 |
| 6[f] | pentane | lyophilized[g] | 42 | 45 | 6 d | 6 |
| 7[f] | pentane | lyophilized[g] | 14 | 15 | 4 d | 27 |
| 8 | buffer | enzyme soln | 24 | 13 | 2 d | < 1 |
| 9[f] | pentane | PCMC[e] | 29 | 31 | 0.5 d | 10 |
| 10[f] | pentane | sol−gel[g] | 29 | 37 | 3 d | 29 |
| 11[e] | pentane | PhosES-01[h] | 25 | 30 | 1 d | 25 |
| 12[e] | pentane | PhosES-02[h] | 34 | 48 | 10 h | 45 |
| **13**[e] | **pentane** | **PhosES-03**[h] | 21 | 26 | 30 h | **116** |
| **14**[f] | **pentane** | **Accurel**[h] | 30 | 41 | 3 h | **68** |
| 15[f] | pentane | Accurel[g] | 52 | 90 | 5 h | 33 |
| 16 | pentane | Eupergit[e] | 30 | 22 | 3 d | 4 |
| 17 | pentane | Eupergit[g] | 34 | 40 | 2 d | 12 |

[a] Reactions were carried as follows: 10 mg of substrate, 5 equiv of *n*-BuOH, and 5 mL of solvent. For each immobilized enzyme reaction, 50 μL of enzyme solution (NaPi buffer pH 7, 100,000 U/mL) was used. For silica, 200 mg immobilized catalyst X 2 was used in each assay; for the PhosES series, 100 mg immobilized catalyst X 2 was used for each assay. [b] 2 mg of freeze-dried enzyme was used. [c] Protein coated microcrystal method ref 17. [d] Reference 19. [e] PhosES01-03 were silica materials given by Phosphonics, Ltd. [f] Accurel adsorption; ref 18. [g] Dry catalyst. [h] Catalyst containing water (see the Experimental Section); for entry 7, 5 equiv of water with respect to substrate added. [i] Conversion determined by GC. [j] Ee of enol ester **13**, determined with chiral HPLC on Chiracel AD column.

**TABLE 2. Screening CAL-B Lipase**




| entry[a] | solvents | immobilization | conversion (%) | (S,S)-enol ester 13 ee[d] (%) | reaction time | *E* value |
|---|---|---|---|---|---|---|
| 1 | buffer | lyophilized[b] | 55 | 69 | 12 h | 7 |
| 2 | hexane | lyophilized[b] | 65 | 60 | 7 d | 3 |
| 3 | toluene | lyophilized[b] | 54 | 78 | 5 d | 11 |
| 4 | toluene | silica[b] | 57 | 85 | 5 d | 12 |
| 5 | pentane | PCMC[c] | 58 | 85 | 30 h | 11 |
| 6 | pentane | Sol−gel[b] | 12 | 11 | 3 d | 10 |
| 7 | pentane | PhosES-01[e] | 21 | 21 | 2 d | 11 |
| 8 | pentane | PhosES-02[e] | 17 | 17 | 2 d | 13 |
| 9 | pentane | PhosES-03[e] | 18 | 20 | 2 d | 26 |
| 10 | pentane | PhosES-03[b] | 34 | 43 | 1 d | 17 |
| 11 | pentane | Accurel[b] | | | 3 d | |
| **12** | **pentane** | **Accurel**[b] | **29** | **40** | **3 d** | **142** |
| 13 | pentane | Eupergit[c] | 29 | 25 | 5 d | 5 |
| 14 | pentane | Eupergit[b] | | | 5 d | |

[a] The reaction protocols are the same as that for *Humicola* lipase when the same supporting material was used. [b] Dry catalyst. [c] Catalyst containing water. [d] Ee of enol ester **13**, determined with chiral HPLC on Chiracel AD column.

in the open conformation at the water−hydrophobic interface.[20] Surface-associated water seems to be essential for high selectivity in our reactions. This may facilitate such a conformational change resulting in increased reactivity and selectivity. If we compare entry 6 with 7 and entry 14 with 15, it can be seen that with free enzyme (entries 6 and 7) or immobilized enzyme (entries 14 and 15), a small amount of water is advantageous; entry 7 is better than 6, and 14 is better than 15.

A similar strategy was applied using Cal-B lipase (Table 2) which catalyzed the reaction with the opposite sense of enantioselectivity giving (*R,R*)-diketone **7** and unreacted (*S,S*)-**13**. Preliminary solvent screening for the lyophilized Cal-B suggested that the best organic solvent was toluene; however, there was no obvious improvement in both activity and enantioselectivity after immobilization on silica (cf. entries 3 and 4). Marginal improvements in selectivity were observed when using the PhosES supports in the presence of water. However, a striking increase in selectivity (entry 12, $E$ = 142) was noted with Accurel under anhydrous conditions.[21] As with the *Humicola* enzyme, the Eupergit support provided no advantage for this reaction system.

On a preparative scale, use of Accurel-supported *Humicola* lipase provided the most practical method. Starting with 9 g of (±)-enol acetate **13**, we obtained 3.5 g (39%) of enantiopure (*R,R*)-**13** (> 99% ee) after 50 h reaction time. The reaction is easy to follow by chiral HPLC allowing optimal recovery of enantiomerically enol ester. The (*S,S*)-diketone **7** was obtained in 59% yield, 65% ee. Immobilized Cal-B on Accurel afforded 30% isolated yield of the antipodal homochiral (*S,S*)-**13**, although the reaction time was considerably longer (18 days). Either enantiomer of the chiral diketone **7** was made in quantitative yield using *Candida rugosa* lipase in buffer to hydrolyze the enol acetate. This lipase was conveniently found to be completely nonselective for either enantiomer of **13**.

In summary, we report an efficient chemoenzymatic approach to homochiral bicyclo[2.2.2]octane-2,5-dione **7**, a key intermediate for the Hayashi diene ligand, precluding the requirement for using preparative chiral HPLC. This method includes a practical 4-step synthetic route for the racemic diketone (60% overall yield) and an enzymatic resolution, in which the racemic diketone **7** is first converted into corresponding mono enol acetate **13** for the lipase-catalyzed resolution. Immobilized lipase *Humicola* sp. lipase and Cal-B lipase gave the enol acetate with enantiocomplementary selectivity and the homochiral diketone **7** is obtained in quantitative yield by hydrolysis with *Candida rugosa* lipase.

## Experimental Section

**Catalyst Preparation (*Humicola* sp. Lipase on Accurel).** In a small sample tube, Accurel (1 g) was vortexed with EtOH (3 mL), allowed to stand for 15 min, and then transferred to a 100 mL conical flask. Sodium phosphate buffer (0.1M, pH 6.0) (20 mL) and *Humicola* sp. lipase solution (200 μL) were added, and the resulting suspension was incubated at 30 °C for 48 h. The mixture was filtered through a Buchner funnel and washed with distilled water (3 × 2 mL). The water saturated Accurel-lipase (3 g) was then ready for use (generally 1 g of Accurel can hold ca. 2 g water). If the catalyst is not used immediately, it should be stored in a tightly stoppered sample tube in the fridge (4 °C). Before use, the catalyst should be vortexed for several minutes to encourage any water condensed on the wall of sample tube back into the catalyst. The dry catalyst was prepared by suction filtration, incubation at 30 °C for 1 day followed by drying under vacuum overnight.

**Catalyst Preparation (Humicola Lipase on PhosphonicS PhosES-03).** To a 100 mL conical flask containing NaPi buffer (25 mM, pH 7.0, 20 mL), PhosphonicS PhosES-03 (1 g), and *Humicola* sp. lipase solution (200 μL) was added. The resulting suspension was incubated at 30 °C for 12 h. The same workup procedure as for Accurel was applied to this mixture to give ca. 1 g of catalyst (the PhosES-03 itself contains about 40 wt % water). Storage and usage of the catalyst was as for the Accurel catalyst described above.

The same procedures were applied for immobilization of Cal-B except that 10 mg of freeze-dried CAL-B was used in place of the *Humicola* sp. lipase solution. The dry catalysts were prepared by suction filtration, incubation at 30 °C for 1 day followed by drying under vacuum overnight.

**PhosES-03-Supported *Humicola* sp. Lipase-Catalyzed Resolution.** Racemic enol acetate **13** (1.0 g, 5.55 mmol) was dissolved in pentane (200 mL). To this mixture was added wet *Humicola* sp. lipase on PhosES-03 enzyme catalyst (1 g) (see above) followed by *n*-BuOH (10 mmol, 740 mg). The reaction finished after 1 day. The reaction was run several times and the yield of enantiomerically pure (*R,R*)-(+)-**13** varied from 320 mg to 400 mg (32- 40% yield) with 68−60% yield of diketone−**7** obtained, after chromatography (hexane/EtOAc 4:1).

**Accurel-Supported CAL-B Lipase-Catalyzed Resolution.** Racemic enol acetate **13** (1.0 g, 5.55 mmol) was dissolved in pentane (200 mL). To this mixture 1 g of wet type CAL-B on Accurel (see above) was added followed by *n*-BuOH (10 mmol, 740 mg). The reaction finished after 18 d. The reaction was run several times, and the yields of enantiomerically pure (*S,S*)-(−)-**13** varied from 280 to 300 mg (28−30% yield), with 72−70% yield of diketone−**7**, obtained after chromatography (hexane/EtOAc 4:1).

**Large-Scale Resolution of (±)-13 Using Accurel-Supported *Humicola* sp. Lipase.** A solution of (±)-2-acetoxybicyclo-[2.2.2]octan-2-en-5-one **13** (9.0 g, 50 mmol), *n*-butanol (3.7 g, 50 mmol), and pentane (1.8 L) was added to a 3 L reactor (see the Supporting Information) in which the immobilized enzyme (made using 8 g of Accurel, see above) was placed on a fabric-covered mesh, alongside anhydrous sodium bicarbonate (2.1 g, 20 mmol) to trap any acetic acid produced. The reaction was stirred for 50 h until the (*R,R*)-enol acetate **13** was >99% ee. The reaction mixture was filtered through cotton wool to remove the immobilized enzyme and bicarbonate. After removal of the solvents, the residue was separated by silica-gel column chromatography (hexane−EtOAc 4:1) to give the enantiomerically pure (>99% ee) (*R,R*)-enol acetate **13** (3.5 g, 39% yield) and (*S,S*)-diketone−**7** (4.1 g, 59.5% yield, 64% ee).

**(*R,R*)-(-) and (*S,S*)-(+)-Bicyclo[2.2.2]octane-2,5-dione 7.** To a 100 mL flask containing 100 mg of (*R,R*)-(+)-**13** was added 50 mL of NaPi buffer (0.1 M, pH 7.5) and 5 mg of crude *Candida rugosa* lipase (Lipase AY). The resulting mixture was stirred for 2 h. The buffer solution was extracted with EtOAc (50 mL × 3). The combined organic extracts were dried over magnesium sulfate followed by filtration and evaporation to give pure (*R,R*)-(−)-**7** (76 mg, 100%) as a white solid: $[\alpha]^{20}_{D} = -43$ (*c* 0.42, $CHCl_3$). The same procedure was used to give (*S,S*)-(+)-**7**: $[\alpha]^{20}_{D} = +44$ (*c* 0.36, $CHCl_3$).

**Acknowledgment.** We thank Dr John Whittall for initial inspiration, EPSRC for the Dorothy Hodgkin Postgraduate Award to Y.L. and PhosphonicS, Ltd. for the kind donation of silica support material PhosES01-03.

**Supporting Information Available:** Experimental details and compound data. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Asymmetric Catalysis**

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# Chemoenzymatic Synthesis and Application of Bicyclo[2.2.2]octadiene Ligands: Increased Efficiency in Rhodium-Catalyzed Asymmetric Conjugate Additions by Electronic Tuning**

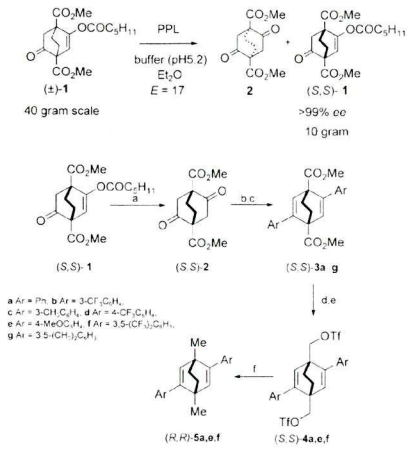
*Yunfei Luo and Andrew J. Carnell**

Chiral dienes are a new class of highly effective ligands, developed independently by Hayashi and Carriera et al., that have shown great promise in the field of asymmetric catalysis for reactions catalysed by rhodium and iridium.[1] A range of synthetically useful transformations have been realized in excellent yield and enantiomeric excess using $C_1$-symmetric and $C_2$-symmetric dienes.[2–10]

However, compared with phosphine ligands and $C_1$-symmetric dienes, the accessibility and structural variation in the most widely employed $C_2$-symmetric [2.2.2] diene ligands has been limited by inflexible synthetic routes and, most notably, the difficulty in resolution of the dienes or their synthetic precursors, which is currently achieved using chiral HPLC separation of the diene or a late-stage intermediate.[1b,2,11–14] As a result, the electronic effects on activity and enantioselectivity in these ligands have not been well studied. Although structural modifications including both electronic and steric changes have been made with the current bicyclic frameworks,[2b,c,5,9d,7] the results have shown that steric factors are dominant. Hayashi et al. have shown that $C_1$-symmetric [2.2.2] dienes in which one alkene was conjugated with an ester group gave a remarkable rate increase in arylation of imines.[9d] In this example it is believed that an electron withdrawing naphthyl ester substituent on one of the alkenes accelerates transmetallation to form a *trans* aryl–rhodium bond.

Although the chiral diene–Rh catalyst allows reactions to be conducted at lower temperatures compared with phosphine ligands, in diene–rhodium-catalyzed arylations with aryl boronic acids generally more than two equivalents of the arylboronic acid are necessary in order to achieve a high yield, and for particularly inactive substrates as many as 5 equivalents.[2b,15,16] This is attributed to the competing protodeboronation side-reaction[17] and indicates that reaction temperature is not the only factor responsible for the low atom efficiency.

Herein we report a chemoenzymatic approach giving access to a new series of chiral 1,4-disubstituted $C_2$-symmetric [2.2.2] diene ligands (Scheme 1).




***Scheme 1.*** Biotransformation of (±)-enol ester **1** with PPL and preparation of 1,4-disubstituted bicyclo[2.2.2] ligands from (*S,S*)-enol ester **1**: a) $Na_2CO_3$, MeOH (99%); b) LHMDS, $Tf_2O$, THF, −78 °C (70%); c) $ArB(OH)_2$, $[Pd(PPh_3)_4]$, Tol/EtOH/aq, $Na_2CO_3$, RT (80–95%); d) $LiAlH_4$, THF, (99%); e) $Tf_2O$, $CH_2Cl_2$/pyridine, −78 °C →RT (99%); f) $LiHBEt_3$, THF, 0 °C→RT (93–99%). LHMDS = lithium hexamethyldisilazide, Tf = trifluoromethanesulfonyl.

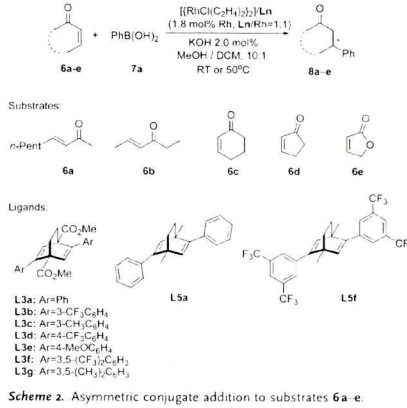
The scalability and ease of operation of the key enzyme resolution step, in addition to high yielding chemical transformations, provides a highly practical route that could quickly satisfy demands for greater quantities. Moreover, a significant electronic effect was observed in the diene ligands for rhodium-catalyzed arylation reactions. Both catalytic activity and, more interestingly from a mechanistic perspective, enantioselectivity depend on the electronic properties of the ligands. In addition, atom efficiency for the aryl boronic acids was correlated.

The key step in the route is a reliable and scalable lipase-catalysed chiral resolution of the (±)-enol ester **1**, derived from the (±)-diketone **2**, which is made from commercially available succinate dimer.[18] After substrate and enzyme screening we found that porcine pancreatic lipase (PPL) in a biphasic system comprising $Et_2O$/citrate buffer (2:1; 100 mM, pH 5.2) gave reasonable selectivity ($E = 17$). The reaction was carried out on 40 g of substrate to afford 10 g of enantiopure enol ester (*S,S*)-**1**.[19] after purification by crystallisation. The crystals were found to be racemic enol ester, with enantiopure (*S,S*)-enol ester **1** remaining in solution, greatly facilitating isolation of the homochiral product. We found that enol ester of lower *ee* can also be purified to homochirality in a single crystallization.[20] Although the *E* value for this enzyme reaction is modest, the scalability and ease of purification make it an extremely attractive method to obtain quantities of the chiral dione (*S,S*)-**2** for our diene ligand synthesis. The antipodal (*R,R*)-**2** can be recovered and crystallized to optical purity through the (*R,R*)-enol ester **1**.[20]

The enantiopure (*S,S*)-dione **2** was obtained in near quantitative yield by methanolysis of the biotransformation product (*S,S*)-enol ester **1**. Formation of the bis-enol triflate was followed by introduction of the aryl substituents by palladium-catalysed cross-coupling to give ligands (*S,S*)-**L3a–g**.[2c,7,21] Lithium aluminum hydride reduction, activation as the ditriflate **4a,e,f** and displacement by superhydride gave (*R,R*)-ligands **L5a,e,f**.

The 1,4-diester ligands (*S,S*)-**L3a–g** (Scheme 1), were evaluated for the asymmetric conjugate addition of phenylboronic acid **7a** to 3-nonen-2-one **6a** using previously reported conditions (Scheme 2, Table 1).[2a,5]

The results for enantioselectivity were not encouraging compared to other [2.2.2] bicyclic ligands.[2i] From a purely structural perspective, it was logical that the substituent ester groups at the 1 and 4-positions may be giving a detrimental effect on the enantioselectivity. However, we also noted an interesting trend that for substrate **6a**, ligands with electron-withdrawing aryl substituents gave better enantioselectivities




***Scheme 2.*** Asymmetric conjugate addition to substrates **6a–e**.

***Table 1:*** Ligand screen for the asymmetric conjugate addition to **6a**.

| Entry[a] | Ln | Ligand 2,5-Aryl | Yield[b] | *ee* **8a**[c] |
|---|---|---|---|---|
| 1 | **L3a** | Ph | 95 | 75 |
| 2 | **L3b** | 3-$CF_3C_6H_4$ | 93 | 83 |
| 3 | **L3c** | 3-$CH_3C_6H_4$ | 98 | 73 |
| 4 | **L3d** | 4-$CF_3C_6H_4$ | 95 | 82 |
| 5 | **L3e** | 4-$MeOC_6H_4$ | 99 | 74 |
| 6 | **L3f** | 3,5-$(CF_3)_2C_6H_3$ | 43 | 89 |
| 7 | **L3g** | 3,5-$(CH_3)_2C_6H_3$ | 96 | 70 |

than those with electron-donating groups, (e.g. comparing entry 2 with 3, entry 4 with 5 and entry 6 with 7 in Table 1).

The methyl ester groups were converted into methyl groups, and ligands **L5a** and **L5f** were evaluated for a range of acyclic and cyclic enones **6a–e** (Scheme 2, Table 2). For substrate **6a**, we were surprised to find a more pronounced difference in enantioselectivity between ligands **L5a** (52% *ee*) and **L5f** (97% *ee*) than between **L3a** (75% *ee*) and **L3f** (89% *ee*) (Table 1). The enantioselectivity improvement between **L3f** (89% *ee*) and **L5f** (97% *ee*) may result from removing a detrimental effect of 1,4-ester groups whilst maintaining the electron withdrawing aryl substituents. However, comparison of the results for **L3a** and **L5a** contradict this, where the 1,4-diester ligand **L5a** out-performs the 1,4-dimethyl ligand **L3a**. Similar results were obtained with substrate **6b** (Table 2, entry 2). Nevertheless, ligand **L5a** gave excellent yields and selectivity for enones **6c–e** affording (*R*)-configured products **8c–e**. Results for cyclohexanone **6c** are similar to those obtained by Hayashi with diene ligand **L5g**.[2c] For the lactone **6e** both yield and *ee* were improved (95%, 98% *ee*) compared with Carreira's carvone derived ligand (80%, 90% *ee*)[3b] and Darses' ligand (56%, 90% *ee*).[15] Unlike **L5a**, ligand **L5f** gives excellent *ee* for both acyclic and cyclic enones in the expected product configuration, which is consistent with the space differentiation model for chiral $C_2$-symmetric diene ligands developed by Hayashi.[2a,c,i,6a,15]

***Table 2:*** Comparison between **L5a** and **L5b** with various substrates.

| Entry[a] | 6 | Prod. 8 | Yield (%)[b] **L5a** | *ee* (%)[c] **L5b** | Config. |
|---|---|---|---|---|---|
| 1 | **6a** | **8a** | 99 [52] | 99 [97] | *S* |
| 2 | **6b** | **8b** | 99 [67] | 99 [95] | *S* |
| 3 | **6c** | **8c** | 98 [99] | 92 [98] | *R* |
| 4 | **6d** | **8d** | 100 [99] | 80 [96] | *R* |
| 5 | **6e** | **8e** | 95 [98] | 76 [92][d] | *R* |

[a] Reaction conditions: **6a** (0.5 mmol), **7a** (0.6 mmol for **L5a**, 1.0 mmol for **L3a–g** and **L5f**), $[\{Rh(C_2H_4)_2Cl\}_2]$ (1.8 mol% Rh), Ligand **Ln** (2 mol%), MeOH/$CH_2Cl_2$; 10:1 (2.3 mL), KOH (2 mol%) (2.3 mL), RT, 1 h for **L5a** and 3 h at 30 °C for **L5f** and **L3a–g**. [b] Yield of isolated product. [c] *Ee* values were determined by chiral HPLC (see Supporting Information). [d] 3.0 equiv of phenylboronic acid used.

[**] We acknowledge Dr. John Whittall for initial inspiration, Dr. Neil Berry for preliminary modeling and the EPSRC for a Dorothy Hodgkin Postgraduate Award to Y.L.

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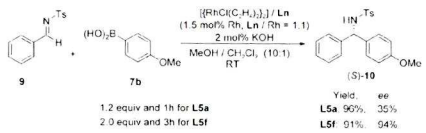
in 1 h with only 1.2 equivalents of phenyl boronic acid, compared with at least 2 equivalents for current diene ligands. The requirement for use of excess arylboronic acid is thought to arise as a result of the competing rhodium-catalysed protodeboronation.[17] This significant and unexpected advantage can reasonably be attributed to the 1,4-dimethyl substitution in ligand **L5a** as compared to Hayashi's ligand **L5g** and other ligands. On the other hand, in order obtain a high yield when using our ligand **L5f**, more than 2 equivalents of phenyl boronic acid was required. For example, the yield of **8e** when using ligand **L5f** was only 76% although 3 equivalents phenyl boronic acid were used (Table 2, entry 5).

The only major difference between ligands **L5a** and **L5f** is that **L5a** is more electron rich. These results suggest that the electronic properties of diene ligands are associated with activity, enantioselectivity (for linear substrates) as well as the productivity (ability to avoid the protodeboronation of aryl boronic acid). Increasing the electron density of the ligand benefits the reactivity and suppresses the protodeboronation reaction, but can undermine the enantioselectivity for linear substrates, as for **L5a**. To retain the high enantioselectivity for the linear substrates requires the ligand not be too electron rich. However, this can sacrifice some reactivity and allow the side reaction, as for **L5f**.

In order to further test this electronic effect, ligands **L5a** and **L5f** were examined for the 1,2-addition to tosyl imine **9**, which can be categorized as a linear substrate (Scheme 3).

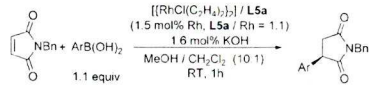



*Scheme 3.* Asymmetric arylation of *N*-tosyl benzylimine **9**.

The results were as expected; as with the 1,4-addition to linear enones, **L5a** gave much higher reactivity but lower *ee* with less arylboronic acid, while **L5f** gave excellent enantioselectivity but lower reactivity and some protodeboronation side-reaction. To the best of our knowledge, this is the first time that such a unique electronic effect has been observed in diene ligands closely linking reactivity, enantioselectivity and productivity.

The asymmetric conjugate addition of aryl boronic acids to *N*-benzyl maleimide (**11**) is known to be a challenging reaction, and the products are synthetically useful.[22] The chiral phosphine ligand, binap, gave only 70% yield and 58% *ee*, while a chiral norbornadiene diene ligand gave 88% yield and 69% *ee*.[2b] The phosphine–alkene hybrid ligands developed by Grützmacher and Hayashi et al. both gave the desired product in high yield with Hayashi's hybrid ligand giving 89–95% *ee*.[15,23] However, multiple equivalents (3 equiv) of arylboronic acid were required to ensure a high yield. Again it was found that ligand **L5a** achieves both high activity and enantioselectivity for the formation of (*R*)-**12a–d** using only 1.1 equivalents of ArB(OH)$_2$ (**7a–d**) at room temperature in 1 h (Scheme 4). This is the most efficient ligand for this transformation to date.

The product resulting from the conjugate addition of phenyl boronic acid to 6-methylcoumarin (**13**) has been used




**7a**: Ar=Ph
**7b**: Ar=4-MeOC$_6$H$_4$
**7c**: Ar=2-CF$_3$C$_6$H$_4$
**7d**: Ar=2-MeO-1-naphthyl

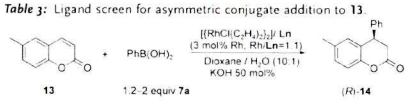
**12a**: 95% yield, 95% *ee*
**12b**: 98% yield, 99% *ee*
**12c**: 92% yield, 99% *ee*
**12d**: 98% yield, 99% *ee*

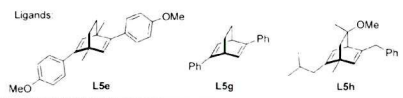
*Scheme 4.* Asymmetric conjugate addition to *N*-benzyl maleimide **11**.

in a synthesis of the urological drug tolterodine.[24] Examples reported by the Hayashi group show that phosphine ligands can give excellent *ee* (>99%), however 10 equivalents of phenylboronic acid were necessary to achieve a high yield.[24] Only one example using a chiral diene for this reaction has been reported by Carreira et al., where 43% yield and 98% *ee* were obtained in the addition of phenylboronic acid to the coumarin at 50 °C using his carvone derived ligand.[3b] We tested our ligands **L5a**, **L5e** and **L5f** and also ran comparative reactions with Hayashi's ligand **L5g** and Carreira's ligand **L5h** (Table 3).

The enantioselectivity for all ligands was uniformly high (98% *ee*). However, a remarkable difference in reaction rate and yield was found between the ligands when comparing conversion and isolated yield at 30 °C and 50 °C after 6 h, and

*Table 3:* Ligand screen for asymmetric conjugate addition to **13**.




| Entry[a] | Ligand | *T* [°C] | *t* [h] | Conv. [%][b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | **L5g** | 30 | 24 | <5 | – | n.d. |
| 2 | **L5g** | 50 | 6 | 40 | 32 | 98 |
| 3 | **L5h** | 30 | 24 | 22 | 20 | 98 |
| 4 | **L5h** | 50 | 6 | 48 | 39 | 98 |
| 5 | **L5a** | 30 | 24 | 66 | 63 | 98 |
| 6 | **L5a** | 50 | 6 | 85 | 72 | 98 |
| 7 | **L5f** | 50 | 24 | 0 | 0 | – |
| 8 | **L5e**[e] | 30 | 3 | 100 | 95 | 98 |

[a] Reaction conditions: Ref. [2c]. [b] Conversion determined by GC (EC-1 column; calibrated with standard **10** and **11**). [c] Yield of isolated product. [d] *Ee* values determined by chiral HPLC. [e] As footnote [a] except 25 mol% KOH and 1.2 equiv PhB(OH)$_2$ were used.

24 h, Hayashi's ligand **L5g** gave the lowest rate of conversion, Carreira's ligand **L5h** gave increased conversion, our **L5a** gave a further increase but the most active ligand for this reaction was ligand **L5e**, containing the 4-methoxyphenyl groups. This gradual increase in reactivity may be attributed to an increase in electron density in the ligand system: Hayashi's diene **L5g** contains no bridge substituents, Carreira's diene **L5h** contains one methyl substituent (but the 2,5-positions are alkyl-substituted rather than aryl), ligand **L5a** has two bridge methyl groups and **L5e** has two bridge methyl groups and electron donating 4-methoxyphenyl substituents. This is corroborated by the fact that our electron-deficient ligand **L5f** gave no reaction for this substrate.

In summary, we have developed an efficient synthesis of the chiral $C_2$-symmetric bicyclic [2.2.2] diene ligand system that enables flexible substitution at the 1- and 4-positions. The synthesis is short, high yielding and includes a practical lipase resolution as a key step that can be done on scale and provides an attractive alternative to resolution by chiral preparative HPLC. We have assessed a new series of 1,4-dimethyl 2,5-diaryl bicyclo [2.2.2] octadiene ligands for rhodium-catalysed asymmetric conjugate addition to a range of cyclic and acyclic enones. The addition of 1,4-methyl substituent groups in the ligands enabled us for the first time to observe a significant electronic effect which affects catalytic performance. The catalysts with electron rich ligands gave excellent activity for all substrates and excellent enantioselectivity for cyclic enones with high atom efficiency (only 1.1–1.2 equiv arylboronic acid), even for a challenging substrate such as 6-methylcoumarin. However, this advantage was not shared by linear enones as far as enantioselectivity is concerned. This problem could be abrogated by introducing electron-withdrawing groups on the ligand to achieve high *ee* for all type substrates, although 2-3 equivalents of arylboronic acid are required to compensate for protodeboronation and to achieve high yield. Mechanistic studies to gain a deeper understanding into this phenomenon are ongoing.

## Experimental Section

General procedure for the Rh–diene-catalyzed asymmetric conjugate addition: To a Schlenk reaction tube [{RhCl(C$_2$H$_4$)$_2$}$_2$] (1.8 mg, 9 μmol of Rh) and diene ligand (10 μmol) in DCM (0.3 mL) were added under a nitrogen atmosphere. The solution was stirred for 5 min followed by addition of 0.2 M KOH/methanol solution (50 μL, 10 μmol). The resultant mixture was stirred for 15 min before addition of methanol (2 mL), arylboronic acid (0.6–1.5 mmol) and enone (0.5 mmol). The reaction mixture was stirred at the required temperature for 1–3 h, then filtered through a silica pad and purified with preparative TLC to give pure product.

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[19] The absolute configuration of the (*S,S*)-enol ester **1** was established by X-ray crystallographic analysis of a bis-ketal bis-triflate derivative (see Supporting Information).

[20] In a non-optimised biotransformation, where the aim was to isolate the unreacted enol ester in high *ee*, the (*R,R*)- dione product **2** (2.5 g, 40% *ee*) was isolated, converted to the enol hexanoate and crystallised to give the single enantiomer (0.84 g, 99.9% *ee* (48% of theory)).

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